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Herpes simplex viruses: new relationships between epidemiology and history

Scientists revise the dating of viral dispersal from Africa: it did not occur during ancient "Out of Africa" migrations, but rather, more recent events, including the transatlantic slave trade of the eighteenth century

An Italian research team has refined the history and origins of two extremely common pathogens in human populations, herpes simplex virus type 1 and type 2.

As many of us may experience, literally on the skin, the common herpes simplex virus type 1 is a primary cause of orofacial lesions. The less prevalent form, herpes simplex virus type 2, is usually responsible for genital herpes. Both viruses can also cause very serious diseases, including non-epidemic encephalitis and neonatal herpes infection. In the latter case, the virus is generally transmitted by the mother during delivery and the consequences can be extremely serious for the infant.

To better understand the origins of the virus, the research team has shown that the evolutionary history of these two viruses is different and more complex than previously thought.

"We analyzed the diversity of the two viruses in relation to their geographical origin," researcher Diego Forni explains, "and what we noticed are that viruses deriving from distinct continents were not particularly different, an observation that is not consistent with the hypothesis of an ancient migration. Our data, however, clearly indicated that the two viruses originated in Africa. We therefore thought it was necessary to estimate when the viral strains circulating today among human populations left the African continent. "

The study, conducted at the IRCCS Medea in collaboration with the University of Milan, has just been published in the advanced online edition of Molecular Biology and Evolution.

Just as for other viruses belonging to the Herpesviridae family (e.g., viruses that cause chickenpox and mononucleosis), herpes simplex viruses type 1 and 2 are very similar to viruses that infect African great apes. In many cases these viruses have evolved together with their hosts and have infected our species since it originated in Africa. To date, Africa remains the continent where herpes simplex viruses type 1 and 2 are most prevalent. This gave rise to the hypothesis that the viral strains that infect us today left Africa in very ancient times. It was thought this coincided during the major "Out of Africa" migratory event that, around 60,000 years ago, led humans to populate all other continents.

"Recently, thanks to the study of viruses found in archaeological remains, the scientific community has a better knowledge of the speed at which viral species evolve," said study co-author Manuela Sironi. "Thus, we can use rather precise methods that allow the dating of viral origin and dispersal. By applying these methods, we estimated that the circulating strains of herpes simplex virus type 1 migrated from Africa about 5000 years ago. The exit from Africa of herpes simplex virus type 2 was even more recent and probably occurred in the eighteenth century."

The type 2 herpes result draws a link between epidemiological data and a major historical event --- the height of the transatlantic slave trade. In this century, millions of people were deported from Africa to the Americas. Most likely, this heinous forced human migration also led to the initial spread of herpes simplex virus type 2 in the Americas. In fact, the prevalence of the virus is higher in this continent than elsewhere and it is second only to Africa.

And herpes simplex virus type 2 is probably not the only pathogen to have been introduced to the American continent as a result of the

slave trade. Previous studies have shown that the same happened for yellow fever virus and for a parasitic worm (Schsitosoma mansoni). For ecological reasons these pathogens remained confined to tropical or subtropical areas. Herpes simplex virus type 2, instead, found no barriers to today's planetary spread.

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A replacement for exercise?

A protein called Sestrin might be responsible for many of the benefits of a good workout

Whether it be a brisk walk around the park or high intensity training at the gym, exercise does a body good. But what if you could harness the benefits of a good workout without ever moving a muscle?

Michigan Medicine researchers studying a class of naturally occurring protein called Sestrin have found that it can mimic many of exercise's effects in flies and mice. The findings could eventually help scientists combat muscle wasting due to aging and other causes.

"Researchers have previously observed that Sestrin accumulates in muscle following exercise," said Myungjin Kim, Ph.D., a research assistant professor in the Department of Molecular & Integrative Physiology.

Kim, working with professor Jun Hee Lee, Ph.D. and a team of researchers wanted to know more about the protein's apparent link to exercise. Their first step was to encourage a bunch of flies to work out.

Taking advantage of *Drosophila* flies' normal instinct to climb up and out of a test tube, their collaborators Robert Wessells, Ph.D. and Alyson Sujkowski of Wayne State University in Detroit developed a type of fly treadmill. Using it, the team trained the flies for three weeks and compared the running and flying ability of normal flies with that of flies bred to lack the ability to make Sestrin.

"Flies can usually run around four to six hours at this point and the normal flies' abilities improved over that period," says Lee. "The flies without Sestrin did not improve with exercise."

What's more, when they overexpressed Sestrin in the muscles of normal flies, essentially maxing out their Sestrin levels, they found those flies had abilities above and beyond the trained flies, even without exercise. In fact, flies with overexpressed Sestrin didn't develop more endurance when exercised.

The beneficial effects of Sestrin include more than just improved endurance. Mice without Sestrin lacked the improved aerobic capacity, improved respiration and fat burning typically associated with exercise.

"We propose that Sestrin can coordinate these biological activities by turning on or off different metabolic pathways," says Lee. "This kind of combined effect is important for producing exercise's effects."

Lee also helped another collaborator, Pura Muñoz-Cánoves, Ph.D., of Pompeu Fabra University in Spain, to demonstrate that muscle-specific Sestrin can also help prevent atrophy in a muscle that's immobilized, such as the type that occurs when a limb is in a cast for a long period of time.

"This independent study again highlights that Sestrin alone is sufficient to produce many benefits of physical movement and exercise," says Lee.

Could Sestrin supplements be on the horizon? Not quite, says Lee. "Sestrins are not small molecules, but we are working to find small molecule modulators of Sestrin."

Additionally, adds Kim, scientists still don't know how exercise produces Sestrin in the body. "This is very critical for future study and could lead to a treatment for people who cannot exercise."

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How police surveillance technologies act as tools of white supremacy

Although surveillance technologies appear to be race-neutral, modern police surveillance technologies do not operate outside racial bias.

by Constantine Gidaris, The Conversation

A 2019 surge of gang-related shootings in Toronto motivated the Ontario government to commit $3 million to double the number of Toronto Police surveillance cameras in the city. The Toronto Police could now go to 74 cameras from 34.

Before that, in the summer of 2018, a spike of gun violence across the city led Toronto Mayor John Tory to urge Toronto Police and city council to adopt a new technology called ShotSpotter. Already in place across major cities in the United States, ShotSpotter is a real-time audio recording system that uses acoustics in public spaces to detect, locate and automatically notify police of gunfire.

But police surveillance technologies tend to be reactionary and focus on street-level crimes. Despite the increased likelihood of discovering drugs on white people rather than Black people, the usual offender stereotype allows police to disproportionately stop and target Black people.

By adhering to racial stereotypes that categorize certain behaviours of Black youth as criminal—simply standing on street corners or being out late at night —police often see youth engaged in these activities as potential criminals. After a few months of deliberation, the Toronto Police and city council abandoned the idea of ShopSpotter, citing numerous legal and privacy concerns. Neither, however, expressed any concern for the ways that ShotSpotter could have been used to exacerbate racial disparities in policing.

News reports frequently characterize technologies as benign instruments of policing designed to help reduce crime. Rarely, though, are they seen as weapons that sustain the white supremacist ideology —the foundation for the institution of policing. According to Sandra Bass, director of the Berkeley Public Service Center, police upheld a legal, formal and informal social order that was premised on a way of "keeping the Negro in his place."

A history of criminalizing Blackness

Acts of racialized policing and surveillance emerged out of slave patrols in the American South during the mid-to-late 1800s. These patrols consisted of mostly white volunteers who took it upon themselves to control, regulate and punish slaves who ventured beyond the plantation. During this time, the Ku Klux Klan also emerged alongside local and state Jim Crow laws, which legalized racial and residential segregation. These informal slave patrols evolved into the more formal police apparatus widely recognized today, enforcing Jim Crow laws until 1965.

In Canada, a similar policing ideology took shape through various mechanisms of segregation. As scholar Robyn Maynard details in her book, *Policing Black Lives*, policing evolves out of a desire to protect the white settler state from the fabricated criminal dangers of Blackness.

In the 19th and 20th centuries, anti-Black hysteria equated Blackness with pathological criminality. Maynard explains that the hyper-surveillance and over-policing of Black communities served to maintain "white dominance across all aspects of Black life."

This exclusion also included restricting or eliminating Black folks from accessing education, employment and housing.

North American-wide government cutbacks to social programs in the 1980s intensified racialized policing and surveillance tactics. These cuts along with new policies drew attention to the enduring myth of Black criminality. Black people were perceived by the state as "lazy and idle" and "scapegoated as freeloaders and possible criminals."

Policing race with technology

Since then, little has changed in the policing of race. Blackness is still viewed as a problem to be contained. Evidence of this is the disproportionate rates of Black incarceration in Canada.

Black people are also over-represented as victims of violent and deadly encounters with Toronto Police as a 2018 report by the Ontario Human Rights Commission details.

The practice of carding—used by the Toronto Police since the 1950s—has unfairly targeted Black people. Years of data shows that young Black men have been stopped and carded "2.5 times more than white males," despite only making up about four percent of the city's population. Crucially, carding has been proven to be an ineffective solution to gun violence.

Although surveillance technologies appear to be race-neutral and lack human bias, modern police surveillance technologies do not operate outside racial and discriminatory systems. Many surveillance systems repeatedly demonstrate racial and systemic bias. And yet, closed-circuit television cameras have repeatedly failed to deter or reduce serious crime, including gun violence. As sociologists Clive Norris and Gary Armstrong have argued, surveillance cameras are not merely about reducing crime. Their research out of London, England, shows that Black youth have been "systematically and disproportionately targeted" by camera operators for no other reason than race.

Not tools but weapons

Like carding, police surveillance technologies such as ShotSpotter can become part of a self-fulfilling prophecy. For example, Toronto Police and city council did not significantly consider in which neighbourhoods ShotSpotter would be deployed by police.

Michael Bryant, executive director and general counsel of the Canadian Civil Liberties Association, feared ShotSpotter would have ended up in lower-income, racialized neighbourhoods already targeted by police. Technologies used by police are not unbiased solutions to crime. For Black communities especially, police can represent the very embodiment of crime itself, linked to extensive histories and ongoing acts of racism, oppression and violence.

Among the police's exhaustive list of lethal and non-lethal weapons, automated surveillance technologies must be further scrutinized. These technologies allow the police to continue to exercise and enforce stealthy but harmful methods of discriminatory policing.

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Common foods can help 'landscape' the jungle of our gut microbiome

Compounds in the foods we eat can trigger phage production

Researchers at San Diego State University have found a new way to harness food as medicine, which has far reaching implications to control harmful microbes in our gut while balancing microbial diversity by fostering the growth of beneficial bacteria.

Foods we eat commonly affect our gut microbiota. New research shows they do so by triggering the production of bacteriophage - viruses that infect and replicate inside bacteria. Compounds in these foods have an antimicrobial effect which causes the phage to replicate.

The researchers began by identifying which foods were antimicrobial, then analyzed them before narrowing it down to a shortlist. When examining growth curves of bacteria, they observed that while bacteria multiply over time, eventually their numbers plateau. However, if phages are activated, then bacterial growth stops altogether and their numbers drop dramatically until they're depleted.

Foods they tested that had antimicrobial effects include honey, licorice, stevia (a sugar substitute derived from the stevia plant), aspartame, hot sauce, herbs such as oregano, spices such as cinnamon and clove, rhubarbs, uva ursi (bear berry), and neem

extract. They also tested toothpaste, since it's known to contain antimicrobial compounds. Of these, honey, stevia, aspartame, neem and uva ursi had the most impact in triggering phage production.

"The microbiome is composed of hundreds of different bacteria and the phages they host," said Lance Boling, an SDSU molecular biologist and research associate. "We could actually tackle certain conditions by adjusting the foods we consume, that will affect microbial diversity which in turn will influence health and diseases." "We also found some foods acted as phage inhibitors and could be used to control pathogenic viruses," Boling added.

Our gut microbiome can affect cognitive ability, metabolism, weight gain or loss, our moods, and even cause depression. It can also cause inflammation that could lead to cancer, diabetes, Crohn's disease and irritable bowel syndrome. With careful analysis and planning, food could be used as medicine to correct imbalances.

"This shows we could sculpt the human gut microbiome with common dietary compounds," said Forest Rohwer, an SDSU microbial ecologist and pioneer of viromics research. "The ability to kill specific bacteria, without affecting others, makes these compounds very interesting." Boling works on microbiome research in Rohwer's lab. Their findings will be published Jan. 13 in *Gut Microbes*.

Identifying phage triggers

When phage replicate they kill the host cell and exit into the environment, which can lead to a cascade effect where they infect bacterial cells around them. Each bacterial cell that bursts - when the phage grows inside them - can have hundreds of new phages that emerge. When they release in the microbiome, if there are more bacteria present, they will continue to infect the bacteria.

"There aren't many known chemical triggers, and we wanted to find these 'prophage' inducers - or what causes the phage DNA to detach and replicate," Boling said.

Once the researchers chose foods with known and perceived antimicrobial effects, they then selected bacteria representative of the two major gut phyla, *Bacteroidetes* and *Firmicutes*, including strains of pathogenic as well as beneficial bacteria. They narrowed the food compounds down to 28 from 117 candidates on which they conducted the prophage induction assay. Bacterial growth was observed with and without food compounds, for comparison. The samples were processed using flow cytometry, a sensitive method for detecting particles as tiny as viruses.

Future applications

While other studies have focused on increasing the abundance of therapeutic phages, this research goes further to explore the reductive effect of 117 commonly consumed foods, chemical additives, and plant extracts on the growth and phage production capacity of common gut bacteria.

This reductive approach is "akin to pulling weeds from a garden so that more desirable plants have room to grow," Boling explained, hence the term 'landscaping' the gut.

Conversely, over-consumption of broad-spectrum antimicrobial foods could contribute to the same metabolic states correlated with low gut diversity that may be produced by the administration of antibiotic medicines. Proper understanding and utilization of these food compounds could aid in the treatment or prevention of conditions associated with gut imbalances, and promote overall health.

"We are excited about finding more prophage inducers and determining the molecular mechanisms by which they work," Rohwer said. "There are probably thousands of compounds that would be useful for eliminating unwanted bacteria."

The researchers recommend that foods found to be prophage inducers should be studied further to elucidate their molecular mechanisms. While the importance of phages and the fact that they

are the most prolific biological entity in the biosphere is well-established, little is understood about the triggers that cause bacteria to produce phage and release them into the environment. Elucidating these mechanisms will further our understanding of how bacteria and phage shape the ecosystems that they populate.

This research was funded by the National Institutes of Health.

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Knee replacement timing is all wrong for most patients

People delay surgery and lose function; others get it too soon with less benefit

CHICAGO --- The timing of knee replacement surgery is critical to optimize its benefit. But 90% of patients with knee osteoarthritis who would potentially benefit from knee replacement are waiting too long to have it and getting less benefit. In addition, about 25% of patients who don't need it are having it prematurely when the benefit is minimal, reports a new Northwestern Medicine study.

This is believed to be the first study to prospectively examine the timeliness of knee replacement among a large number of patients with knee osteoarthritis who could benefit from the surgery. Few prior studies have quantified timeliness of surgery but only among patients who already had knee replacement, and these studies generally were in smaller cohorts of patients.

"People are waiting and waiting to have the procedure and losing the most benefit," said lead investigator Hassan Ghomrawi, associate professor of surgery at Northwestern University Feinberg School of Medicine. African-Americans delayed knee replacement surgery more than Caucasians, the study found.

"When people wait too long, two things happen," Ghomrawi said. "The osteoarthritis causes deterioration of their function. Some of them wouldn't be able to straighten out their legs, affecting their walking and mobility. When you can't get exercise, you can start to develop other health problems such as cardiovascular problems. You may also become depressed. The overall impact can be huge."

The second problem with delaying surgery is less benefit. "You don't get as much function back when you wait too long; your mobility is still reduced versus somebody who had it in a timely fashion," Ghomrawi said. The ideal timing of knee replacement surgery is based on an algorithm that factors in pain, joint function, radiographic assessment and age to determine if a person will benefit from surgery.

Getting knee replacement surgery too early based on the algorithm means patients are having major surgery with risk of complications and getting minimal benefit. They may also need a revision (second surgery) later in life, which is a much more difficult surgery with poorer outcomes than the original surgery. The study will be published Jan. 13 in the *Journal of Bone and Joint Surgery*.

Nearly 1 million knee replacement procedures are performed in the U.S. each year with projections of a rapid increase by 2030, the paper reports.

"As the number of surgeries rises, we need to make sure the timing is optimal for patients to obtain the most benefit and to keep health care costs down," Ghomrawi said. "Because knee replacement is an elective procedure, the timing of surgery is susceptible to not just clinical factors but also demographic, socioeconomic and sociocultural ones. We need to develop a better understanding of these factors to improve timing of surgery."

The Northwestern study was based on 8,002 participants who had or were at risk for knee osteoarthritis and were followed for up to eight years as part of two diverse multicenter trials, the Osteoarthritis Initiative and Multicenter Osteoarthritis.

Dr. Leena Sharma of Northwestern is a study coauthor.

The study was funded by grants R21-AR069867 and P30-AR072579 from the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health.

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Machine keeps human livers alive for one week outside of the body

May increase the number of available organs for transplantation

Researchers from the University Hospital Zurich, ETH Zurich, Wyss Zurich and the University of Zurich have developed a machine that repairs injured human livers and keeps them alive outside the body for one week. This breakthrough may increase the number of available organs for transplantation saving many lives of patients with severe liver diseases or cancer.

Until now, livers could be stored safely outside the body for only a few hours. With the novel perfusion technology, livers - and even injured livers - can now be kept alive outside of the body for an entire week. This is a major breakthrough in transplantation medicine, which may increase the number of available organs for transplantation and save many lives of patients suffering from severe liver disease or a variety of cancers. Injured cadaveric livers, initially not suitable for use in transplantation, may regain full function while perfused in the new machine for several days. The basis for this technology is a complex perfusion system, mimicking most core body functions close to physiology. The corresponding study was published on January 13 in the scientific journal *Nature Biotechnology*.

Offering what other machines cannot

"The success of this unique perfusion system - developed over a four-year period by a group of surgeons, biologists and engineers - paves the way for many new applications in transplantation and cancer medicine helping patients with no liver grafts available" explains Prof. Pierre-Alain Clavien, Chairman of the Department of Surgery and Transplantation at the University Hospital Zurich (USZ). When the project started in 2015, livers could only be kept on the machine for 12 hours. The seven-day successful perfusion of poor-quality livers now allows for a wide range of strategies, e.g. repair of preexisting injury, cleaning of fat deposits in the liver or even regeneration of partial livers.

Liver4Life: A project from Wyss Zurich

The Liver4Life project was developed under the umbrella of Wyss Zurich institute, which brought together the highly specialized technical know-how and biomedical knowledge of experts from the University Hospital Zurich (USZ), ETH Zurich and the University of Zurich (UZH). "The biggest challenge in the initial phase of our project was to find a common language that would allow communication between the clinicians and engineers," explains Prof. Philipp Rudolf von Rohr, Professor of Process Engineering at ETH Zurich and co-leader with Professor Clavien of the study now published in Nature Biotechnology.

Technology with great potential

The inaugural study shows that six of ten perfused poor-quality human livers, declined for transplantation by all centers in Europe, recovered to full function within one week of perfusion on the machine. The next step will be to use these organs for transplantation. The proposed technology opens a large avenue for many applications offering a new life for many patients with end stage liver disease or cancer.

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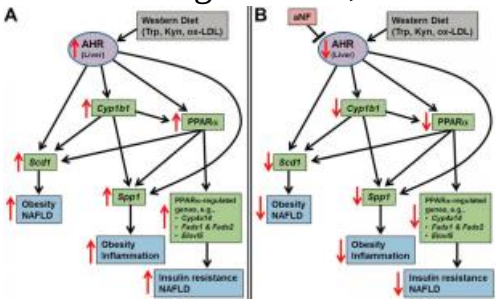
New mechanism may safely prevent and reverse obesity

Researchers at Dartmouth's Norris Cotton Cancer Center observed that blocking a cellular receptor not only prevented but reversed obesity, with no ill side effects, in mice.

LEBANON, NH - Obesity, a global epidemic, is a known contributor to several cancers, including breast, colon, and pancreatic. Stopping the obesity epidemic could be a critical aid in preventing and treating numerous cancers. Researchers with the laboratory of Craig Tomlinson, PhD, at Dartmouth's and Dartmouth-Hitchcock's Norris

Cotton Cancer Center have found a critical target in this cause. The team discovered that a receptor found in almost all cells, called AHR, and known primarily to combat exposures to environmental chemicals, also plays a big role in the body's metabolism. Blocking AHR not only prevented, but reversed obesity in study mice. The team's findings, "Reversal of obesity and liver steatosis in mice via inhibition of aryl hydrocarbon receptor and altered gene expression of CYP1B1, PPARα, SCD1, and osteopontin," are newly published in the International Journal of Obesity.

"We carried out experiments showing that when a drug named NF and known to block the AHR, was added to a high-fat diet, mice did not become any fatter than mice on a low-fat control diet," says Tomlinson. "Mice on the high-fat diet with no NF became very obese within the same time span. No ill effects were observed from the drug."



This is a model depicting AHR-based obesity in liver. **Craig Tomlinson, PhD**

The team then asked whether blocking the AHR with NF could not only prevent obesity but reverse it. "In these experiments, we allowed the mice to become obese on a high-fat diet, and then half the mice were switched to the high-fat diet containing the AHR blocker NF. Over the next few weeks, the mice switched to the high-fat diet containing NF dropped to the same body weight as those mice on the low-fat diet. The remaining mice on the high-fat diet became obese. Again, no ill effects were observed," explains Tomlinson.

Finally, Tomlinson's team investigated the mechanisms behind how the AHR, when blocked by NF, prevented and reversed obesity. Using previous knowledge that the AHR regulates key genes in fat metabolism, the team discovered that in liver cells and in fat cells, the AHR, when blocked by NF, fails to induce several key genes required for fat storage and synthesis. They concluded that the prevention and reversal of obesity from blocking the activity of the AHR is due to key genes regulated by the AHR that are involved in fat metabolism. "Few to no studies have shown that obesity can be reversed by a drug treatment; it is even rarer to know the underlying cellular mechanism," notes Tomlinson.

Tomlinson's team has begun investigating several key questions, including those around the dietary compounds in the food we eat that activate the AHR to cause obesity, and the role that gut bacterial play regarding the AHR and obesity. Most importantly, they have initiated a clinical trial to determine whether the AHR may serve as a therapeutic target to reduce obesity in humans. "We are beginning to understand how the blockage of the AHR prevents and reverses obesity, which may lead to a therapeutic treatment of obesity in humans," says Tomlinson.

Craig Tomlinson, PhD, is a Senior Research Scientist/Analyst/Engineer, Associate Director for Shared Resources, Director of the Genomics Shared Resource, and Member of the Cancer Biology & Therapeutics Research Program at Dartmouth's and Dartmouth-Hitchcock's Norris Cotton Cancer Center. His laboratory research focuses on the common theme of using high-throughput genomics approaches to study gene/environment interactions in development and disease.

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Meteorite Grains Are the Oldest Known Solid Material on Earth

The oldest dust sample, perhaps 7 billion years old, predates the formation of our planet and the sun

By Jay Bennett

A little more than 50 years ago, on September 28, 1969, a meteorite crashed near the rural village of Murchison in Victoria, Australia. Witnesses saw a fireball streak through the sky and break into three pieces just before 11 a.m. local time, followed by an audible tremor in the area. Locals came upon several fragments of the meteorite,

the largest of which, with a mass of 680 grams, crashed through a roof and landed in a pile of hay. All together, some 100 kilograms of the Murchison meteorite were recovered and sent to scientific institutions around the world.

"The Murchison meteorite is a wonderful resource for the scientific community," says Philipp Heck, a curator of meteorites at the Field Museum in Chicago, which houses a large portion of the extraterrestrial object. "It contains some of the oldest condensates in the solar system and also presolar materials."

Some of those presolar materials—microscopic grains that formed before the sun, measuring about 2 to 30 micrometers across—have been dated at 4.6 to 4.9 billion years old. And one of the grains analyzed in a study published today in the *Proceedings of the National Academy of Sciences* is estimated to be roughly 7 billion years old, making it the oldest known material on Earth.

A chunk of the Murchison meteorite at the Smithsonian's National Museum of Natural History. (Basilicofresco via Wikicommons under CC BY-SA 3.0)

"The oldest one is about 3 billion years older than the sun, [which] makes it about 7 [or 7.5] billion years old," says Heck, the lead author of the study. The sun formed about 4.6 billion years ago, and Earth formed about 4.54 billion years ago.

Fifty presolar grains were analyzed in the new study, and the research team was able to estimate the ages of 40 of them. The majority, about 60 percent, predated the solar system by 300 million years or fewer, according to the study. Only a few grains, about 8 percent, were found to be more than a billion years older than the solar system, making them the oldest material ever dated. These grains were originally separated from Murchison meteorite fragments at the University of Chicago over 30 years ago, but they were preserved so future scientists could study them with modern dating technologies.

"We use a different variety of chemical reagents, including acids, to dissolve away silicates and everything that formed in the solar system to get that acid-resistant fraction of presolar dust," Heck says. He describes the method as "burning down the haystack to find the needle," and while some presolar material is lost in the process, the technique has yielded tens of thousands of presolar grains, but only about 100 "large ones."

"Large" is a relative term in this case, considering that the entire mass of material analyzed in the new study is just 300 nanograms, or 300 billionths of a gram. To date the tiny amount of material, the researchers looked for the abundance of certain atoms formed by cosmic rays hitting the dust grains.

To date the material, the researchers used a unique technique to measure the effects of cosmic rays hitting the grains. "When these grains flow through space, they're exposed to cosmic rays, [and] the galactic cosmic rays that they are exposed to are predominantly high-energy protons," Heck says. "Most of them, they just fly through the solid grain. But rarely there is an interaction, [and] one of those protons can hit an atom in the grain."

The team measured the remnants from cosmic ray protons hitting silicon carbide molecules and breaking the silicon atoms into different components. "The silicon can be split into helium and neon," Heck says. "We can take that grain and place it in a mass spectrometer, and we heat the grain with a laser, release the gas and simply count the neon atoms and the helium atoms. By the type of isotope of helium and the type of isotope of neon we can then determine if they were produced by cosmic rays or not. And when we know how many cosmic ray-produced helium and neon atoms we have, we can calculate an age, because the production rate is pretty constant over time."

This dating technique, counting the remnant atoms from collisions with cosmic rays, has been tested in particle accelerators to confirm that it can provide an accurate age estimation. Heck compares it to "putting out a bucket in a rainstorm, then measuring how much water accumulated, and then we can tell how long it was outside. It only works if the rainfall is constant over time, and that's luckily the case with cosmic rays."

However, other dating techniques, such as comparing the isotope ratios left behind by decaying radioactive materials, cannot yet be used to provide an absolute date for these ancient dust grains. And the older the material, or the smaller the grain, the higher the uncertainty in the dating estimate.

Scanning electron micrograph of a dated presolar silicon carbide grain. The grain is about 8 micrometers on its longest dimension. **(Image courtesy of Janaína N. Ávila)**

"There is a large uncertainty because there is a lot of modeling involved in determining those ages," says Pierre Haenecour, an assistant professor with the University of Arizona's Lunar and Planetary Laboratory who studies meteorites and interstellar dust grains but was not involved in the new study. The rate that cosmic rays hit the material, for example, and the number of times that those interactions split the silicon atoms need to be estimated. "It's not a straightforward way of measuring isotopic abundance and getting an age directly from that measurement. So it's a difficult estimate. But still, knowing that [some] of those grains are at least 300 million years older than anything in the solar system is … confirming that they are indeed the oldest solids in the solar system."

As for the oldest grain, Haenecour says, "I think it is difficult to really actually know that this grain is 7 billion years old," but adds that it does appear to be much older than the other grains in the study.

Heck and colleagues also hypothesize that the majority of the grains in the study could have formed during a period of active star formation about 7 billion years ago, which would have produced large amounts of dust roughly 4.6 to 4.9 billion years ago—the same age as most of the grains. Those dust grains, formed somewhere in the Milky Way, clumped together and eventually made their way into the disk of gas and dust around the newborn sun, where they mixed with material that aggregated into an asteroid. Billions of years later, a chunk of that asteroid crashed into Australia. Only about five percent of meteorites contain presolar grains, and in those unique space rocks, the presolar material only accounts for a few parts per million of all the grains in the meteorite.

In the future, Heck and others will isolate more presolar grains from meteorites such as Murchison and continue to date them using the cosmic ray technique. With more grains, researchers can refine their age estimates to further test the accuracy of the method. And researchers also could improve spectroscopy techniques to possibly measure uranium and lead isotope ratios to get an absolute age, similar to how terrestrial rocks are dated, Haenecour says.

"With this study we are just starting this journey of exploring the history of the galaxy with meteorites," Heck says. "The amazing thing is we have a rock in our collection that we just take out of the cabinet and learn something about the history of our galaxy."

http://bit.ly/2Rq4v7V

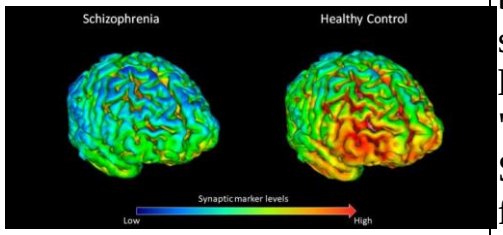
New study finds evidence for reduced brain connections in schizophrenia

Advances in scanning have allowed researchers for the first time to show lower levels of a protein found in the connections between neurons in the living brains of people with schizophrenia

Advances in scanning have allowed researchers for the first time to show lower levels of a protein found in the connections between neurons in the living brains of people with schizophrenia.

The researchers, who conducted the scans at the psychiatric imaging facility at the Medical Research Council (MRC) London Institute of Medical Sciences, say these changes could underlie the cognitive difficulties seen in schizophrenia and provide targets for research into new treatments.

It was first hypothesised in the early 1980s that schizophrenia was caused by dysfunctional synapses - where the nerve signals are transmitted between neurons in the brain. However, researchers had only been able to study this indirectly, such as in post mortem brains samples, or animal and cell models in the lab.



PET brain scans showing that 18 healthy volunteers (right) have on average higher levels (shown by yellow-red) of synapse marker protein SV2A than 18 participants with schizophrenia (left). **Credit E. Onwordi at MRC London Institute of Medical Sciences (LMS))**

In this study, published in *Nature Communications*, the researchers detected this in living brains for the first time by utilising a tracer that emits a signal which can be picked up by a PET brain scan. After being injected, the tracer binds specifically to a protein found in synapses called SV2A (synaptic vesicle glycoprotein 2A), which has been shown in animal and post-mortem studies to be a good marker of the density of synaptic nerve endings in the brain.

They scanned 18 adults with schizophrenia and compared them to 18 people without schizophrenia.

They found that levels of the synaptic protein SV2A were lower in the front parts of the brain - regions of the brain involved in planning - in people with schizophrenia.

Professor Oliver Howes, who led the study, from the MRC London Institute of Medical Sciences, Imperial College London and King's College London, said: "Our current treatments for schizophrenia only target one aspect of the disease - the psychotic symptoms - but the debilitating cognitive symptoms, such as loss of abilities to plan and remember, often cause much more long-term disability and there's no treatment for them at the moment. Synaptic loss is thought to underlie these symptoms.

"Our lab at the MRC London Institute of Medical Sciences is one of the few places in the world with this new tracer, which means we've been able for the first time to show there are lower levels of a synaptic protein in people with schizophrenia. This suggests that loss of synapses could underlie the development of schizophrenia.

"We need to develop new treatments for schizophrenia. This protein SV2A could be a target for new treatments to restore synaptic function."

Dr Ellis Onwordi, who conducted the research, from the MRC London Institute of Medical Sciences, Imperial College London and King's College London, said: "Schizophrenia is a highly debilitating disorder, and the therapeutic options are too limited for many patients. To develop better treatments in the future we need studies like this to shine a light on how the extraordinarily complex wiring of the human brain is altered by this disease."

"Having scans that can characterise the distribution of the approximately 100 trillion synapses in the living brain, and find differences in their distribution between people with and without schizophrenia, represents a significant advance in our ability to study schizophrenia."

The people with schizophrenia who were scanned had all received antipsychotic medication, so the researchers wanted to exclude this as a factor in the synaptic dysfunction. They gave antipsychotic

drugs, haloperidol and olanzapine, to rats for 28 days and found it had no effect on the levels of the protein SV2A.

Professor Howes said: "This is reassuring as it's suggesting that our antipsychotic treatments aren't leading to loss of brain connections.

"Next we hope to scan younger people in the very early stages to see how synaptic levels change during the development of the illness and whether these changes are established early on or develop over time."

The researchers were funded by the Medical Research Council, part of UK Research and Innovation, and Wellcome. They were also supported by the National Institute for Health Research Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London.

http://bit.ly/3arPECH

Gut bacteria could guard against Parkinson's, study finds

A common bacteria that boosts digestive health can slow - and even reverse - build-up of a protein associated with Parkinson's, new research suggests.

Building on previous research linking brain function to gut bacteria, this study in a Parkinson's model of roundworms, identified a probiotic - or so-called good bacteria - which prevents the formation of toxic clumps that starve the brain of dopamine, a key chemical that coordinates movement. These new findings could pave the way for future studies that gauge how supplements such as probiotics impact the condition.

In the brains of people with Parkinson's, alpha-synuclein protein misfolds and builds up, forming toxic clumps. These clumps are associated with the death of nerve cells responsible for producing dopamine. The loss of these cells causes the motor symptoms associated with Parkinson's, including freezing, tremors and slowness of movement.

The researchers from the Universities of Edinburgh and Dundee used roundworms altered to produce the human version of alpha-synuclein that forms clumps. They fed these worms with different types of over-the-counter probiotics to see if bacteria in them could affect the formation of toxic clumps.

The scientists found that a probiotic called Bacillus subtilis had a remarkable protective effect against the build-up of this protein and also cleared some of the already formed protein clumps. This improved the movement symptoms in the roundworms. The researchers also found that the bacteria was able to prevent the formation of toxic alpha-synuclein clumps by producing chemicals that change how enzymes in cells process specific fats called sphingolipids.

The study by Goya ME, Xue F, et al, published in the journal Cell Reports, was funded by Parkinson's UK, the EMBO and the European Commission. It is the latest in a number of recent studies which have found a link between brain function and the thousands of different kinds of bacteria living in the digestive system, known as the gut microbiome. Other studies into mice have found that the gut microbiome has an impact on the motor symptoms.

Lead researcher, Dr Maria Doitsidou, from the Centre for Discovery Brain Sciences at the University of Edinburgh, said: "The results provide an opportunity to investigate how changing the bacteria that make up our gut microbiome affects Parkinson's. The next steps are to confirm these results in mice, followed by fast-tracked clinical trials since the probiotic we tested is already commercially available."

Dr Beckie Port, Research Manager at Parkinson's UK, said: "Parkinson's is the fastest growing neurological condition in the world. Currently there is no treatment that can slow, reverse or protect someone from its progression but by funding projects like this, we're bringing forward the day when there will be.

"Changes in the microorganisms in the gut are believed to play a role in the initiation of Parkinson's in some cases and are linked to

certain symptoms, that's why there is ongoing research into gut health and probiotics.

"The results from this study are exciting as they show a link between bacteria in the gut and the protein at the heart of Parkinson's, alpha synuclein. Studies that identify bacteria that are beneficial in Parkinson's have the potential to not only improve symptoms but could even protect people from developing the condition in the first place."

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Notes to editors

This press release highlights the findings reported in a paper published on Tuesday 14th January at 16:00 2020.

Probiotic Bacillus subtilis Protects against α-Synuclein Aggregation in C. elegans' - published in Cell Reports. https://dx.doi.org/10.1016/j.celrep.2019.12.078

http://bit.ly/30Cu1em

Unfruitful: Eating more produce will not cure, stop prostate cancer

Diets bolstered by more vegetables produced no extra protection from the increased micronutrients

National guidelines recommend that men with prostate cancer eat a vegetable-rich diet, suggesting it might decrease cancer progression and death. But in a Phase III randomized clinical trial, patients with prostate cancer assigned to eat seven or more servings of vegetables and fruits daily saw no extra protection from the increased consumption of micronutrients.

"These data indicate that, despite prevailing scientific and public opinion, eating more vegetables will not alter the course of prostate cancer. It will not, to the best of our knowledge, suppress or cure it," said J. Kellogg Parsons, MD, University of California San Diego School of Medicine and Moores Cancer Center professor of urology and study lead investigator. "However, while eating a healthy diet rich in fruits and vegetables and getting more exercise may not cure cancer, it may keep the body stronger and healthier, which may help patients tolerate cancer treatments."

The Men's Eating and Living (MEAL) study, published January 14, 2020 in the *Journal of the American Medical Association* and led by UC San Diego Moores Cancer Center and Roswell Park Comprehensive Cancer Center investigators, enrolled 478 men aged 50 to 80 years at 91 sites in the United States. The patients had been diagnosed with early-stage prostate adenocarcinoma and enrolled in an active surveillance program in which patients defer immediate treatment until the disease advances.

Patients were randomized to a control group that received written information about diet and prostate cancer or to a telephone counseling behavioral intervention program that encouraged participants to eat foods high in carotenoids, such as leafy greens, carrots and tomatoes, and cruciferous vegetables such as broccoli and cabbage. Both groups were monitored for two years.

"Patients assigned to the intervention increased their intake of fruits and vegetables to a statistically significant degree, and significantly more than control patients did. These findings were supported by significant changes in the blood carotenoid levels of patients. Nonetheless, these data fail to support prevailing assertions in clinical guidelines and the popular media that diets high in micronutrient-rich vegetables improve cancer-specific outcomes among prostate cancer survivors," said James Marshall, PhD, Distinguished Professor with the Department of Cancer Prevention and Population Sciences at Roswell Park, co-senior author on the study with John Pierce, PhD, Professor Emeritus of Cancer Prevention at UC San Diego School of Medicine.

The study is the first randomized clinical trial to test the effect of dietary intervention on prostate cancer. It was conceived based on preliminary scientific data and on inquiries from patients who

wondered if a change in diet would influence their diagnosis or treatment, said Parsons, a urologic oncologist at UC San Diego Health, San Diego's only National Cancer Institute-Designated Comprehensive Cancer Center.

"The most common question I receive from men on active surveillance is, 'Can I decrease the chances that I will need treatment for prostate cancer by changing my diet?' We now have good evidence that a diet rich in fruits and vegetables and light on red meat is not likely to impact need for treatment," said co-author James Mohler, MD, professor of oncology with Roswell Park's department of urology. "But this study does not provide justification for eating anything you want, either. The overall health benefits of a diet that's relatively low in fat and rich in fruits, vegetables and healthy grains are well-established."

The impact of nutrition on diseases is an ongoing conversation among researchers and clinicians. Scientific studies have identified a strong role for changing diet to improve outcomes in diabetes and cardiovascular disease, but not in cancer, said Parsons.

Although the MEAL study revealed no positive impact on prostate cancer, it did demonstrate that behavioral modification can lead patients to make healthier food choices, said Parsons.

"We designed a simple and inexpensive program that proved we could change people's diets for the better. We hoped that through nutrition we could alter disease outcomes and then use those data to build a network of diet counselors to help men with prostate cancer eat more vegetables," said Parsons. "It's still an endeavor worth considering, possibly in patients with advanced prostate cancer."

Co-authors include: Donna E. Hansel, Loki Natarajan, Martha White and Sheri J. Hartman, UC San Diego; David Zahrieh, Heshan Liu and Elizabeth M. Storrick, Mayo Clinic; Electra Paskett, Ohio State University; Adam S. Kibel, Harvard Medical School; Olwen Hahn and John Taylor, University of Chicago; Sean P. Stroup, Naval Medical Center San Diego; Peter Van Veldhuizen, Midwest Oncology Associates; Lannis Hall, Washington University; Eric J. Small, UC San Francisco; and Michael J. Morris, Memorial Sloan Kettering Cancer Center.

https://wb.md/2txnEq1

Carb Restriction a Viable Choice for Reversal of Type 2 Diabetes?

Carbohydrate restriction is a viable patient choice for type 2 diabetes reversal, according to Sarah Hallberg, DO.

Doug Brunk

LOS ANGELES — "Nutritional ketosis supports diabetes reversal by reducing insulin resistance while providing an alternative fuel to glucose with favorable signaling properties," she said at the World Congress on Insulin Resistance, Diabetes, and Cardiovascular Disease.

Low-carbohydrate nutritional patterns including ketosis have extensive clinical trial evidence for improvement of type 2 diabetes, including preliminary results from a 5-year study of 465 patients enrolled in the Indiana Type 2 Diabetes Reversal Trial that Dr. Hallberg is overseeing in her role as medical director and founder of the medically supervised weight-loss program at Indiana University Health Arnett, Lafayette.

"The ketogenic diet is not a fad diet, it's what we used to treat people with before the advent of insulin," said Dr. Hallberg, who has been recommending and counseling patients with type 2 diabetes to follow a ketogenic diet for nearly 10 years. "Of course, insulin has been wonderful. It's saved so many people with type 1 diabetes. But we also misused it in type 2 diabetes. Instead of counseling people the way we used to about the food that they're taking in to control their blood sugar, we've just been putting [them] on medication, including insulin."

The American Diabetes Association and other organizations have updated their guidelines to include low-carbohydrate eating patterns for type 2 diabetes treatment, she continued. Veterans Affairs/Department of Defense recommend carbohydrate levels as low as 14%.

Dr. Hallberg, who is also medical director for Virta Health, defined a very-low-carbohydrate or ketogenic diet as less than 50 g of carbohydrates per day, or fewer than 10% of calories consumed. A low-carbohydrate diet is 51-130 g of carbohydrates per day, or 25% or fewer calories consumed, whereas anything above 25% calories consumed is not a low-carbohydrate diet. A well-formulated ketogenic diet, she continued, consists of 5%-10% carbohydrates (or less than 50 g), 15%-20% protein, and 70%-80% fat. The carbohydrates include 5-10 g per day of protein-based food, 10-15 g of vegetables, 5-10 g of nuts/seeds, 5-10 g of fruits, and 5-10 g of miscellaneous nutrients. "When we're talking about a total carbohydrate intake per day of under 50 g, you can get a lot of vegetables and nuts in," she said. "I like to tell my patients they're not eating GPS: no grains, no potatoes, and no sugar."

Recently, Dr. Hallberg and colleagues published a review in which they sought to evaluate the appropriateness of sources cited in the ADA's guidelines on eating patterns for the management of type 2 diabetes, identify additional relevant sources, and evaluate the evidence (Diabetes Obes Metab. 2019;21[8]:1769-79). "We looked at how much evidence there is for the low-carb diet, the Mediterranean diet, the DASH [Dietary Approaches to Stop Hypertension] diet, and a plant-based diet," she said. "We found a wide variation in the evidence for each eating pattern, but the low-carb eating pattern for diabetes has so much more evidence than any of the other eating patterns."

In an earlier study, researchers followed 10 inpatients with diabetes in a metabolic ward for 3 weeks. Their mean age was 51 years, and their mean body mass index was 40.3 kg/m^2. The patients were fed a standard diet for 7 days, then a low-carbohydrate diet (21 g per day) for 14 days (*Ann Intern Med*. 2005; 142[6]:403-11). After 2 weeks of the low-carbohydrate diet, their mean fasting blood glucose dropped from 7.5 to 6.3 mmol/L, and their mean hemoglobin A_{1c} (HbA_{1c}) fell from 7.3% to 6.8%. "The levels came down very fast," said Dr. Hallberg, who was not involved with the study. "This is an important part of the intervention, because when you get a patient who's tried everything, who's injecting hundreds of units of insulin every day, you can make a huge difference in the first couple of weeks. It is not unusual for us to pull patients off of 200-plus units of insulin. This is as motivating as all get out. It also affects their pocketbook right away. This is one of the reasons our patients are able to sustain a ketogenic diet along with support: early motivation and satisfaction."

In a longer-term trial, researchers evaluated the impact of a ketogenic diet in 64 obese patients with diabetes over the course of 56 weeks (*Moll Cell Biochem*. 2007;302[1-2]:249-56). The body weight, body mass index, and levels of blood glucose, total cholesterol, LDL cholesterol, triglycerides, and urea showed a significant decrease from week 1 to week 56 (*P* less than .0001), while the level of HDL cholesterol increased significantly (*P* less than .0001).

A separate trial conducted in Israel evaluated the effects of a low-carbohydrate diet, compared with a Mediterranean or low-fat diet in 322 moderately obese patients over the course of 2 years (*N Engl J Med*. 2008;359:229-41). The rate of adherence to a study diet was 85% at 2 years. The mean weight change was greatest for those on the low-carbohydrate diet, followed by the Mediterranean and low-fat diets. Fasting glucose was best for those on the Mediterranean diet at the end of 2 years, whereas change in HbA_{1c} was best among those on the low-carbohydrate diet.

Another study randomized patients to a low-carbohydrate ketogenic diet (less than 20 g per day with no calorie restriction) or to a low–glycemic index diet (55% carbohydrate restriction of 500 kcal from baseline) over the course of 24 weeks (*Nutr Metab [Lond]*. 2008 Dec 19. doi:10.1186/1743-7075-5-36). Between baseline and week

24, the mean HbA_{1c} fell from 8.8% to 7.3% in the very-low-carbohydrate diet group, and from 8.3% to 7.8% in the low–glycemic diet group, for a between-group comparison *P* value of .03. In addition, 95% of patients in the low-carbohydrate diet group were able to reduce or eliminate the number of medications they were taking, compared with 62% of patients in the low–glycemic diet group (*P* less than .01).

Dr. Hallberg and colleagues are currently in year 4 of the 5-year Indiana Type 2 Diabetes Reversal Study, a prospective, nonrandomized, controlled trial of carbohydrate restriction in 465 patients, making it the largest and longest study of its kind. Of the 465 patients, 387 are in the continuous-care arm, which consists of a diet from Virta Health based on principles of nutritional ketosis, and 87 patients in a usual care arm who are followed for 2 years. The trial includes patients who have been prescribed insulin and who have been diagnosed with diabetes for an average of 8 years.

At the meeting, Dr. Hallberg presented preliminary results based on 2 years of data collection. The retention rate was 83% at 1 year and 74% at 2 years. In the treatment arm, the researchers observed that the level of beta hydroxybutyrate, or evidence of ketogenesis, was the same at 2 years as it had been at 1 year. "So, people were still following the diet, as well as being engaged," she said.

At the end of 2 years, the mean HbA_{1c} reduction was 0.9, the mean reduction for the Homeostatic Model Assessment of Insulin Resistance was 32%, and 55% of completers experienced reversal of their diabetes. Overall, 91% of insulin users reduced or eliminated their use of insulin, and the average weight loss was 10% of baseline weight. "Medication reduction was across the board," she added. "This is huge from a cost-savings and a patient-satisfaction standpoint. We were improving A_{1c} levels in patients who have had diabetes for an average of over 8 years while we were getting [them] off medication, including insulin. Low carb is now the standard of care."

Even patients who did not experience a reversal of their diabetes were conferred a benefit. They had an average reduction of 1.2 in HbA_{1c} level, to 7%; their average weight loss was 9.8%; 45% of patients eliminated their diabetes prescriptions; 81% reduced or eliminated their use of insulin; there was an average reduction of 27% in triglyceride levels; and they had a 17% reduction in their 10-year risk score for atherosclerotic cardiovascular disease.

In the overall cohort, the 10-year Atherosclerotic Cardiovascular Disease risk score improved by 12%; almost all markers for cardiovascular disease improved at 1 year. "We were giving these patients appropriate support, which I think is key," Dr. Hallberg said. "No matter what you do, you have to have a high-touch intervention, and supply that through technology. We do better than medication adherence. Putting patients on a carbohydrate-restricted diet with the appropriate support works for sustainability."

Dr. Hallberg disclosed that she is an employee of Virta Health and that she is an adviser for Simply Good Foods.

This article first appeared on MDEdge.com

http://bit.ly/2tvPo4O

Scientists Discovered 'Mini-Computers' in Human Neurons—and That's Great News for AI

Neurons in our cortex seem to have uniquely evolved to sustain incredibly complex computations in their input cables

By Shelly Fan

With just their input cables, human neurons can perform difficult logic calculations previously only seen in entire neural networks. To restate: human neurons are far more powerful devices than originally thought. And if deep learning algorithms—the AI method loosely based on the brain that's taken our world by storm—take note, they can be too.

Those are unconventional, fighting words.

For 70 years, neurons were considered the basic computational unit of the brain. Yet according to a new study published this month in *Science*, the neurons in our cortex, the outermost "crust" of our brain, seem to have uniquely evolved to sustain incredibly complex computations in their input cables. It's as if someone finally obtained proof that your computer's electrical wiring is actually made up of mini-processors, each performing calculations before sending results to a CPU.

It's weird. It's controversial. But it has also just been seen for the first time in human neurons.

As the authors conclude: we long assumed that a neuron could only operate logical functions such as AND and OR, whereas more complex computations required entire networks. We find that activity in a neuron's input cables can support complex logical operations using completely different rules than a single neuron.

So why should we care? Fundamentally, it has to do with intelligence—why we stand out among the animal kingdom, and how we can potentially replicate that intelligence with AI.

Like the Earth's crust, the cortex is also made up of multiple layers, with distinctive wiring patterns that link up neurons within layers and among different ones. Neuroscientists have long thought that our enormously intricate cortex contributes to our intellectual capabilities—in fact, deep learning was inspired by computations embedded within cortical neurons.

But the new results, recorded from surgically-removed brain chunks from patients with brain tumors and epilepsy, suggest that current deep learning methods are only scratching the surface of replicating our brain's computations. If AI systems can incorporate these newly discovered algorithms, they could potentially become far more powerful.

Meet the All-or-None Neuron

A textbook neuron looks like a leafless tree: massive roots, called dendrites, lead to a sturdy, bulbous base—the body. Like water and nutrients, incoming electrical signals shoot up dendritic roots into the body, where a hump-like structure synthesizes all the information. If the stimulation is sufficiently strong, it gets passed down a singular tree trunk—the output cable called an axon—then transmitted to another neuron by way of bubbles filled with chemical messengers or with electricity. If the input signals are too weak, the neuron kills the data. It's why neuroscientists often call single neurons "binary" or "digital": they either fire or don't.

Simple, no?

Well…not quite. For decades, a question nagged at the back of neuroscientists' minds: why are dendritic trees, compared to a single lonely axon, so much more intricate?

By recording from single neurons in rodent brains, scientists recently began figuring out that dendritic trees aren't just simple passive cables. Rather, they're extremely active components underlying a hidden layer of neural computation. Some dendritic trees, for example, can generate electrical spikes five times larger and more frequently than classic neuronal firing. Just in rats, the discovery of active dendrites mean that the brain could have 100 times more processing capacity than previously thought.

The new study asks: does the same hold true for humans?

Human Dendrites Are Special

Compared to rodent brains, the multi-layered human cortex is much thicker and denser. Layers 2 and 3 (L2/3) especially stand out for their elaborate and densely-packed dendritic forests. Compared to other species—or even the rest of the human brain—these layers contain a disproportionate amount of neuronal matter. The root cause of this strange thickening lies in our genes, which encode a brain development program to guide the characteristic. Some even

believe that it's fundamental to what makes us human. If dendrite "inputs" help shape our neurons' computation—and our intelligence—then L2/3 is where we should be able to observe them, the authors reasoned.

Measuring electrical activity from dendrites, each 100 times smaller than the diameter of a human hair, is much easier said than done. It's partly why these enormously powerful calculations have been hard to capture using electrodes even in animals—the process is similar to gently sucking on an ant's back with a Roman column-sized straw without hurting the ant.

Rather than recording from a living, intact human brain, the team opted to look at fresh slices of the cortex removed due to epilepsy or tumors. It's a smart strategy: slices are much easier to examine using traditional neuroscience methods—for example, something called a "patch clamp" that records directly from neuronal components. Slices can also be examined under the microscope using fluorescent dyes that glow during activity. Using brain tissue from two different types of patients can then help weed out signals unique to each brain disease to get to the root of human dendritic computations.

A bizarre signal immediately emerged. Human dendrites sparked with activity, but the electrical spikes quickly dissipated as they traveled towards the cell body. In contrast, a standard neural signal doesn't taper down as it gallops along the output cable towards its next destination. Even weirder, the dendritic signals relied strictly on calcium ions to generate their electricity, which massively differs from classic neural signaling.

It's like suddenly discovering a new species that consumes carbon dioxide, rather than oxygen, to sustain its activity—except that species is part of you. These signals, dubbed "dCaAPs," have never been observed in cortical cells from any mammals previously, the authors said.

"There was a 'eureka' moment when we saw the dendritic action potentials for the first time," said study co-author Dr. Matthew Larkum at Humboldt University of Berlin. "The experiments were very challenging, so to push the questions past just repeating what has been done in rodents already was very satisfying."

But it gets weirder. Unlike a neuron's all-or-none firing, human dendrites seem to go analogue. That is, their response is "graded," but in an unintuitive way: the *stronger* their stimuli, the *lower* their response. This is in stark contrast to other neuronal computations, where stronger input, even from multiple sources, usually leads to stronger output. And while these dendritic spikes aren't loners *per se*—a few dCaAPs helped change the firing of its neuron—many of the dendrite's electrical activity seemed to do their own thing.

Forest in the Trees

Cataloging the secret lives of human dendrites is already interesting, but the authors went a step further to ask what it all means.

Using computational modeling, they recreated dCaAPs' unique firing pattern and challenged it to solve a logic function called XOR. It compares two inputs, and if the bits are the same, the result is 0. If they're different, it results in 1. Unlike the simpler AND and OR functions, XOR normally requires an entire neural network to perform.

However, human dendrites' strange behavior, where one input only leads to one output, allowed them to "effectively compute the XOR operation," the authors said. When stacked together with a neuron's normal AND and OR functions, it's then possible to condense entire network functions into that of a single neuron. However, for now the idea remains theoretical—the authors weren't able to model an entire neuron along with dendritic computations.

But keep your eye out for updates. The results, if validated in intact human brains, hold enormous possibilities for improving deep learning algorithms. For now, deep learning uses individual

artificial "neurons" that link into multi-layered networks—similar to our previous understanding of human brains. Adding dendritic computations could in theory massively expand deep learning capabilities. In a way, AI is now neuroscience's theoretical playground, a collaboration made in heaven.

Regardless, the results peel back another onion layer towards understanding and replicating our intelligence. "Dendrites make up 95 percent of the surface area of pyramidal cells in the cortex, but have remained 'unexplored territory' in the human brain," said Dr. Michael Häusser at University College London, who was not involved in the study. By hunting for similar signals in rodent brains, we may be able to determine whether "the special electrical properties of human dendrites play a key role in making human brains special," he said.

https://go.nature.com/30zqq0p

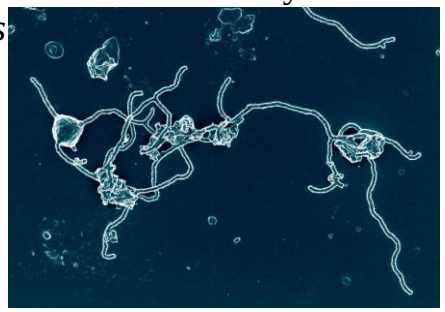
The life of archaea

Cultivation of Asgard archaea brings us closer to understanding how complex life evolved.

Hilaire Belloc's 'The Microbe' opens with the words:

The microbe is so very small / You cannot make him out at all.

The poem lists the wonders of microorganisms, and they continue to reveal their secrets to researchers more than a century after his book *The Bad Child's Book of Beasts* (1896) excited and delighted children. In 2015, researchers published the metagenome of a member of the Asgard group of archaea called Lokiarchaeota (A. Spang *et al. Nature* 521, 173–179; 2015).



A false-coloured electron-microscopy image of an archaeon cultured in the lab. **Hiroyuki Imachi, Masaru K. Nobu and JAMSTEC**

These are descended from an ancient lineage of archaea, simple cells lacking a nucleus and distinct from bacteria. This discovery was exciting because the genes were found to have similarities with those of eukaryotes — the group of organisms whose cells have nuclei and other structures, and which include plants, fungi, humans and other animals. That suggested a stronger connection between archaea and eukaryotes than had previously been thought.

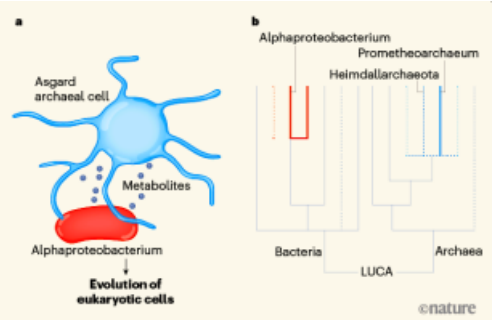


Figure 1 | The evolution of eukaryotic cells. *Imachi et al.[1] report that they have cultured a microorganism, which they call 'Prometheoarchaeum syntrophicum', in the laboratory. The microbe belongs to a group known as Asgard archaea. This is the first time that an Asgard archaeon has been cultured, and has revealed previously unknown aspects of its cellular biology, including the presence of long protrusions. This development might shed light on how complex eukaryotic cells evolved.* ***a****, It is thought that an ancient Asgard archaeon interacted with a bacterium from the class Alphaproteobacteria, for example by exchanging metabolite molecules (grey circles). The mitochondrion, the energy-generating organelle of eukaryote cells, is thought to have evolved when such a bacterium was taken up in the archaeal cell.* ***b****, This simplified evolutionary tree includes branches of the lineages (Proteobacteria shown in red and Asgard archaea in blue) that might have contributed to the formation of eukaryotic cells. Dashed lines on the evolutionary trees represent lineages identified only by genomic analysis and not by organisms cultured in the laboratory. It is thought that eukaryotic cells evolved from a partnership between an alphaproteobacterium and a relative of a Heimdallarchaeote (neither of which is known). LUCA: the last universal common ancestor (the cell(s) from which bacteria and archaea evolved).*

Now, after a heroic effort that took 12 years, researchers led by Hiroyuki Imachi, a microbiologist at the Japan Agency for Marine-Earth Science and Technology, Yokosuka, have successfully grown a new Asgard lineage (H. Imachi *et al. Nature* https://doi.org/10.1038/s41586-019-1916-6; 2020). This

achievement puts to rest concerns that the genes sequenced in 2015 were the result of contamination, or the initial sample being a mix of cells.

Imachi and his colleagues grew cells from sediment that had been collected below the sea bed. But why did the cells take so long to grow? The problem in culturing cells from sediment is that most microbes aren't as obliging as familiar lab workhorses such as *Escherichia coli*. The researchers took up the challenge and with much patience, trial and error, they found that the cells grew best on a diet of peptides, amino acids and even baby-milk powder.

The resulting cells are tiny spheres 300–750 nanometres in diameter, but they often extrude longer, branched filaments that reach out to meet neighbouring bacteria. The researchers think that such a partnership, both biochemical and physical, could tell us more about the processes that led to the eukaryote cell being formed — a question more researchers must surely try to tackle.

Despite the promise of what is to come, a degree of caution is needed. Eukaryotes evolved more than two billion years ago, possibly coincident with an episode of global climatic change called the Great Oxidation Event. Nonetheless, the achievement brings us closer to meeting living relatives of our ancestors. We await the next chapter with anticipation.

Nature ***577****, 294 (2020) doi: 10.1038/d41586-020-00087-4*

http://bit.ly/36aRF2p

Whooping cough evolving into a superbug

Australia needs a new whooping cough vaccine to ensure our most vulnerable are protected from the emergence of superbug strains, new UNSW research has shown.

The current vaccine, widely used since 2000, targets three antigens in the bacteria of the highly contagious respiratory disease which can be fatal to infants. All babies under six months old - in particular, newborns not protected by maternal immunisation - are at risk of catching the vaccine-preventable disease because they are either too young to be vaccinated or have not yet completed the three-dose primary vaccine course.

Australia's whooping cough epidemic from 2008 to 2012 saw more than 140,000 cases - with a peak of almost 40,000 in 2011 - and revealed the rise of evolving strains able to evade vaccine-generated immunity.

In a series of UNSW studies, with the latest published today in *Vaccine*, UNSW researchers took this knowledge further and showed, in a world-first discovery, that the evolving strains made additional changes to better survive in their host, regardless of that person's vaccination status. They also identified new antigens as potential vaccine targets.

First author and microbiologist Dr Laurence Luu, who led the team of researchers with Professor Ruiting Lan, said whooping cough's ability to adapt to vaccines and survival in humans might be the answer to its surprise resurgence despite Australia's high vaccination rates.

"We found the whooping cough strains were evolving to improve their survival, regardless of whether a person was vaccinated or not, by producing more nutrient-binding and transport proteins, and fewer immunogenic proteins which are not targeted by the vaccine," Dr Luu said.

"This allows whooping cough bacteria to more efficiently scavenge nutrients from the host during infection, as well as to evade the body's natural immune system because the bacteria are making fewer proteins that our body recognises. "Put simply, the bacteria that cause whooping cough are becoming better at hiding and better at feeding - they're morphing into a superbug."

Dr Luu said it was therefore possible for a vaccinated person to contract whooping cough bacteria without symptoms materialising.

"So, the bacteria might still colonise you and survive without causing the disease - you probably wouldn't know you've been infected with the whooping cough bacteria because you don't get the symptoms," he said. "Another issue with the vaccine is that immunity wanes quickly - so, we do need a new vaccine that can better protect against the evolving strains, stop the transmission of the disease and provide longer lasting immunity."

Vaccination still key but new vaccine needed

Prof Lan said while he would like to see a new vaccine developed and introduced in the next five to 10 years, the research team's important discovery did not render Australia's whooping cough vaccine redundant.

"It is critical that people are vaccinated to prevent the spread of whooping cough - the current vaccine is still effective for protecting against the disease - but new vaccines need to be developed in the long-term," Prof Lan said. "We need more research to better understand the biology of the whooping cough bacteria, how they cause disease and what proteins are essential for the bacteria to cause infection, so that we can target these proteins in a new and improved vaccine. "This will all help to future-proof new vaccines against the evolving whooping cough strains."

Dr Luu agreed it was crucial that Australia maintained its high vaccination coverage for whooping cough.

"Although the number of whooping cough cases has increased during the past decade, it's still nowhere near as high as what it was before the introduction of whooping cough vaccines," Dr Luu said.

"Therefore, we emphasise that Australia must maintain its high vaccination coverage to protect vulnerable newborns who are not protected by maternal immunity and cannot complete the three-dose primary vaccine course until they are six months old.

"So, vaccination is especially important for children, people who are in contact with children and pregnant women who need the vaccine to produce antibodies to protect their newborns from developing whooping cough in the first few weeks of life."

In addition to babies under six months having a high risk of catching the disease, the elderly, people living with someone who has whooping cough and people who have not had a booster in the past 10 years, are also most at risk.

Whooping cough is characterised by a "whooping" sound and sufferers find it difficult to breathe. The disease is more common during spring and spreads when an infected person coughs or sneezes and other people breathe in the bacteria.

Find the UNSW Sydney research team's related papers here:

Surfaceome analysis of Australian epidemic Bordetella pertussis reveals potential vaccine antigens

Proteomic Adaptation of Australian Epidemic Bordetella pertussis

Comparison of the Whole Cell Proteome and Secretome of Epidemic Bordetella pertussis Strains

http://bit.ly/2TBpdnS

Study shows lactate may prompt cancer formation

The byproduct of glucose may be catalyst that turns mutated cells to cancer

AURORA, Colo. - A byproduct of glucose called lactate, used by every cell in the body, may also prompt a mutated cell to become cancerous, according to new research from the University of Colorado Anschutz Medical Campus. The study was published Tuesday in the journal *Frontiers in Oncology*.

"We discovered that lactate is a catalyst that triggers a mechanism in mutated cells necessary to continue the cancer forming process," said Iñigo San Millán, assistant professor of medicine at the University of Colorado School of Medicine and the University of Colorado Colorado Springs. "This opens a new door to better understand cancer at the metabolic level. It also means we might be able to target lactate with new therapies."

Lactate is not a waste product but a major source of energy for the cell, especially the mitochondria.

The role of lactate in cancer was first described nearly a century ago when Nobel Laureate Otto Warburg discovered that cancer cells were characterized not only by how quickly they consumed glucose, but a marked increase in lactate production. The process was called `The Warburg Effect.'

But exactly how it worked remained a mystery. In 2017, San Millán and his colleague from the University of California, Berkeley, George Brooks, PhD, published a hypothesis they believe explained for the first time the meaning and purpose of the Warburg Effect - to produce lactate for cancer formation purposes.

San Millán, who specializes in metabolism, and his team, sought to demonstrate this hypothesis. They exposed human breast cancer cells to glucose which then produced lactate. The lactate increased the expression of all the main mutated genes involved in breast cancer between 150-800%.

It's well known that not every mutated cell becomes cancerous and there has been speculation on what factors might `trigger' the expression of mutated genes. This study demonstrates that lactate is a key trigger. Now, San Millán and his team are reproducing this study in other cancers like small-cell lung cancer and non-small-cell lung cancer and finding similar results.

"Lactate, which used to be considered a waste product, turns out to be a major signaling molecule and a major regulator of the genes involved in cancer," San Millán said. "This is not the same behavior of lactate we get from doing exercise because that is quickly removed by the muscles and has positive signaling properties to improve physical fitness. The lactate produced in cancer stays put, is constantly being produced and acts as a catalyst to activate mutated genes into cancer. We still don't know these mechanisms but we are investigating them now."

Human muscle tissue is largely resistant to the formation of cancer. Exercise actually reduces the risks of some cancers and even could treat them therapeutically. San Millán has already started applying personalized exercise programs to cancer patients as part of their cancer rehabilitation and is exploring mechanisms by which exercise can help prevent and treat cancer. He's also trying to find ways to block lactate from leaving the cancer cell.

"When lactate is produced it has to leave the cell through a transporter," he said. "We are trying to block the transporter as well as lactate production inside the cancer cell with different compounds. If you block the door, the lactate cannot leave and the cancer cell will burst."

But trying to block lactate in a human with a systemic drug would be deadly, so more targeted treatments are called for. Furthermore, lactate from cancer cells seems to be a key player in keeping the immune system from attacking cancer cells, which is a typical characteristic of cancer. San Millán and his team are currently doing trying to block lactate in different cancers implanted in mice.

"If we can effectively target lactate," he said. "We could possibly be taking a great step toward ending cancer."

https://go.nature.com/2TARECs

Supercomputer scours fossil record for Earth's hidden extinctions

Palaeontologists have charted 300 million years of Earth's history in breathtaking detail.

Ewen Callaway

Palaeontologists have a fuzzy view of Earth's history. An incomplete fossil record and imprecise dating techniques make it hard to pinpoint events that happened within geological eras spanning millions of years. Now, a period that saw a boom in animal complexity and one of Earth's greatest mass extinctions is coming into sharp focus.

Using the world's fourth most powerful supercomputer, Tianhe II, a team of scientists based mostly in China mined a database of more than 11,000 fossil species that lived from around 540 million to 250 million years ago. The result is a history of life during this period, the early Palaeozoic era, that can pinpoint the rise and fall of species during diversifications and mass extinctions to within about 26,000 years. It is published on 16 January in *Science*[1].

"It is kind of amazing," says Peter Wagner, a palaeontologist and evolutionary biologist at the University of Nebraska–Lincoln, who was not involved in the work. Being able to look at species diversity on this scale is like going from a system where "people who lived in the same century are considered to be contemporaries, to one in which only people who lived during the same 6-month period are deemed to be contemporaries", he writes in an essay accompanying the study[2].

Such a view, Wagner adds, will help scientists to identify the causes of mass extinctions — such as the event at the end of the Permian period, some 252 million years ago, that wiped out more than 95% of marine species — as well as understand less dramatic species die-offs and rebounds that have been hard to uncover because of gaps in the fossil record. Understanding these processes could reveal parallels to the planet's current loss of biodiversity.

Patchy record

Most organisms in Earth's history didn't leave fossils, and scientists have identified only a tiny fraction of those that did. As a result, it can be hard to tell whether changes in the fossil record mark real shifts, such as mass extinctions, or are simply caused by a lack of fossil finds.

In the 1960s, palaeontologists began analysing the fossil record systematically, revealing multiple mass extinctions and periods during which life flourished. But these and later efforts could usually pinpoint biodiversity changes only to within about ten million years, because fossils were lumped into relatively long geological periods and analysed en masse.

To improve on this, a team led by palaeontologist Jun-xuan Fan at Nanjing University in China created and analysed a database of fossil marine invertebrate species that were found in more than 3,000 layers of rock, mostly from China but representing geology across the planet during the early Palaeozoic. The group then used software to measure when individual species had emerged and gone extinct.

The program took advantage of the fact that species were usually found in multiple rock formations — each spanning hundreds of thousands to millions of years — and used this information to place upper and lower limits on the period in which the species actually existed. The effort revealed for how long, and in what order, all 11,000 species had existed. It took the supercomputer around seven million processor hours.

Extinctions elucidated

Using this approach, the team was able to learn extra details about well-documented events, such as the end-Permian extinction and the Cambrian explosion in animal diversity around 540 million years ago. The analysis showed, for instance, that species diversity declined in the 80,000 years leading up to the end-Permian mass extinction, which itself occurred over around 60,000 years.

The findings also cast doubt on the existence of a smaller-scale die-off known as the end-Guadalupian extinction, which is thought to have wiped out many marine species around 260 million years ago. That was the biggest surprise, says Mike Benton, a palaeontologist at the University of Bristol, UK, who has documented changes in vertebrate diversity during that period. The study, he adds, "represents a pretty amazing big-data endeavour".

Benton hopes to see the effort extended to later periods — particularly the past 100 million years. Palaeontologists disagree

over whether an apparent increase in animal diversity in this period is the result of sampling bias. “This last 100 million years has been at the heart of a long-running debate about ‘pull of the recent’ and discriminating between real signal and bias,” Benton says.

Norman MacLeod, a palaeontologist at the University of Nanjing and a co-author of the study, says the team’s work might help to reveal the underlying causes of changes in biodiversity, by charting its ups and downs on a timescale that can be matched with environmental and climatic shifts.

Wagner adds that the team’s approach will be most valuable in uncovering — and explaining — smaller-scale extinctions, not dissimilar to those occurring today. Such extinctions could turn out to be “a bad 100,000 years, or a bad week” for some groups of organisms but not others, he says. “When you get this resolution, it starts opening the doors to actually testing what the smaller-turnover events might be like.”

doi: 10.1038/d41586-020-00117-1 ***References***

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http://bit.ly/2NCRYNm

Earth bacteria may have colonised other solar systems

Astronomers suggest microbes might hitch lifts on interstellar asteroids.

By Barry Keily

Could the Earth be a life-exporting planet? That’s the curious question examined in a recent paper written by Harvard University astronomers Amir Siraj and Abraham Loeb.

The researchers take a novel twist on the controversial notion of panspermia – the idea, propelled into the mainstream in the early 1970s by astronomers Fred Hoyle and Chandra Wickramasinghe, that life might have started on Earth through microbes arriving from space. The theory is generally discounted, although eminent astrophysicists such as Stephen Hawking conceded it was at least possible, and a major paper published in 2018 revived the topic big-time.

In their paper, Siraj and Loeb reverse the standard assumption about the direction of the microbial journey and ask whether it is possible to that at some point Earth-evolved bacteria could have been propelled away from the planet, possibly to be deposited somewhere else in the Milky Way.

To examine the idea, they fed several bits of evidence, and a few reasonable assumptions, into a computer and let the numbers run.

First and foremost, they rely on evidence from several studies that confirm the existence of airborne microbial colonies as high as 77 kilometres above the surface of the planet. The authors note that “the abundance of microbes in the upper atmosphere is poorly constrained”, so the density of life in the upper reaches remains largely guesswork.

Also unknown at this point is whether bacteria colonies persist above 100 kilometres up. In the absence of any extraterrestrial versions of dirt-sampling spacecraft such as Japan’s Hayabusa asteroid-lander, the only viable transport methods for shipping microbes out of Earth’s atmosphere, the researchers say, are long-period comets and interstellar objects.

The comets, they note, “can easily be ejected from the Solar System by gravitational interactions with planets due to their low gravitational binding energies and planet-crossing orbits”. Interstellar objects are new to the scenario, their existence well demonstrated by the recent discoveries of ‘Oumuamua and 2I/Borisov – both high-speed big lumps of rock that entered the solar system from elsewhere.

At particular speeds and particular angles, they calculate, both comets and asteroids could come close enough to Earth to “graze” its upper atmosphere before being flung out of the Solar System with the aid of a gravitational slingshot generated by the close

encounter. During such an interaction, the objects would inevitably plough through the airborne bacterial colonies – the researchers cite *Bacillus subtilis*, *Deinococcus radiodurans*, *Escheria coli*, and *Paracoccus denitrificans* as the most likely candidates.

Sufficient numbers of the newly gathered passengers, the modelling shows, would survive the g-forces of the slingshot acceleration and the friction-induced heating caused by leaving the atmosphere.

Siraj and Loeb calculate that across the life of Earth, between one and 10 comets and between one and 50 interstellar objects have come close enough to graze the atmosphere.

Previous research has shown that bacteria could easily survive on board an asteroid or comet in interstellar space – lapsing into suspended animation if necessary – and could just as easily survive the enormous pressure caused by their transport smacking into a planet.

Thus, the researchers conclude that although much more research is needed – particularly into the make-up and distribution of microbes in the upper atmosphere – the idea of panspermia beginning on this planet and heading outwards is "realistic".

The truth of the matter might never be known, of course, at least for several centuries; but it is at least possible that somewhere many light years hence there is a corner of a distant solar system that is forever Earth. The paper can be found on the pre-print site *arXiv*.

https://nyti.ms/2NHEvUl

Bricks Alive! Scientists Create Living Concrete

"A Frankenstein material" is teeming with — and ultimately made by — photosynthetic microbes. And it can reproduce.

By Amos Zeeberg

For centuries, builders have been making concrete roughly the same way: by mixing hard materials like sand with various binders, and hoping it stays fixed and rigid for a long time to come.

Now, an interdisciplinary team of researchers at the University of Colorado, Boulder, has created a rather different kind of concrete — one that is alive and can even reproduce.

Minerals in the new material are deposited not by chemistry but by cyanobacteria, a common class of microbes that capture energy through photosynthesis. The photosynthetic process absorbs carbon dioxide, in stark contrast to the production of regular concrete, which spews huge amounts of that greenhouse gas.

Photosynthetic bacteria also give the concrete another unusual feature: a green color. "It really does look like a Frankenstein material," said Wil Srubar, a structural engineer and the head of the research project. (The green color fades as the material dries.)

Other researchers have worked on incorporating biology into concrete, especially concrete that can heal its own cracks. A major advantage of the new material, its creators say, is that instead of adding bacteria to regular concrete — an inhospitable environment — their process is oriented around bacteria: enlisting them to build the concrete, and keeping them alive so they make more later on.

The new concrete, described Wednesday in the journal Matter, "represents a new and exciting class of low-carbon, designer construction materials," said Andrea Hamilton, a concrete expert at the University of Strathclyde, in Scotland.

To build the living concrete, the researchers first tried putting cyanobacteria in a mixture of warm water, sand and nutrients. The microbes eagerly absorbed light and began producing calcium carbonate, gradually cementing the sand particles together. But the process was slow — and Darpa, the Department of Defense's speculative research arm and the project's funder, wanted the construction to go very quickly. Necessity, happily, birthed invention.

Dr. Srubar had previously worked with gelatin, a food ingredient that, when dissolved in water and cooled, forms special bonds

between its molecules. Importantly, it can be used at moderate temperatures that are gentle on bacteria. He suggested adding gelatin to strengthen the matrix being built by the cyanobacteria, and the team was intrigued.

The researchers bought Knox brand gelatin at a local supermarket and dissolved it in the solution with the bacteria. When they poured the mixture into molds and cooled it in a refrigerator, the gelatin formed its bonds — "just like when you make Jell-O," Dr. Srubar said. The gelatin provided more structure, and worked with the bacteria to help the living concrete grow stronger and faster.

After about a day, the mixture formed concrete blocks in the shape of whatever molds the group used, including two-inch cubes, shoe box-size blocks and truss pieces with struts and cutouts. Individual two-inch cubes were strong enough for a person to stand on, although the material is weak compared to most conventional concretes. Blocks about the size of a shoe box showed potential for doing real construction.

"The first time we made a big structure using this system, we didn't know if it was going to work, scaling up from this little-bitty thing to this big brick," said Chelsea Heveran, a former postdoc with the group — now an engineer at Montana State University — and the lead author of the study. "We took it out of the mold and held it — it was a beautiful, bright green and said 'Darpa' on the side." (The mold featured the name of the project's funder.) "It was the first time we had the scale we were envisioning, and that was really exciting."

When the group brought small samples to a regular review meeting with officials from Darpa, they were impressed, Dr. Srubar said: "Everyone wanted one on their desk."

Stored in relatively dry air at room temperature, the blocks reach their maximum strength over the course of days, and the bacteria gradually begin to die out. But even after a few weeks, the blocks are still alive; when again exposed to high temperature and humidity, many of the bacterial cells perk back up.

The group can take one block, cut it with a diamond-tipped saw, place half back in a warm beaker with more raw materials, pour it in a mold, and begin concrete formation anew. Each block could thus spawn three new generations, yielding eight descendant blocks.

The Department of Defense is interested in using the reproductive ability of these "L.B.M.s" — living building materials — to aid construction in remote or austere environments. "Out in the desert, you don't want to have to truck in lots of materials," Dr. Srubar said.

The blocks also have the advantage of being made from a variety of common materials. Most concrete requires virgin sand that comes from rivers, lakes and oceans, which is running short worldwide, largely because of the enormous demand for concrete. The new living material is not so picky. "We're not pigeonholed into using some particular kind of sand," Dr. Srubar said. "We could use waste materials like ground glass or recycled concrete."

The research team is working to make the material more practical by making the concrete stronger; increasing the bacteria's resistance to dehydration; reconfiguring the materials so they can be flat-packed and easily assembled, like slabs of drywall; and finding a different kind of cyanobacteria that doesn't require the addition of a gel.

Eventually, Dr. Srubar said, the tools of synthetic biology could dramatically expand the realm of possibilities: for instance, building materials that can detect and respond to toxic chemicals, or that light up to reveal structural damage. Living concrete might help in environments harsher than even the driest deserts: other planets, like Mars.

"There's no way we're going to carry building materials to space," Dr. Srubar said. "We'll bring biology with us."

http://bit.ly/2G06BpI

Zika virus' key into brain cells ID'd, leveraged to block infection and kill cancer cells

Working independently, two different UC San Diego research teams identified the same molecule -- αvβ5 integrin -- using brain organoids, tumor organoids and mouse models

Zika virus infection can stunt neonatal brain development, a condition known as microcephaly, in which babies are born with abnormally small heads. To determine how best to prevent and treat the viral infection, scientists first need to understand how the pathogen gets inside brain cells.

Employing different approaches to answer different questions, two research teams at University of California San Diego School of Medicine independently identified the same molecule -- αvβ5 integrin --as Zika virus' key to entering brain stem cells.

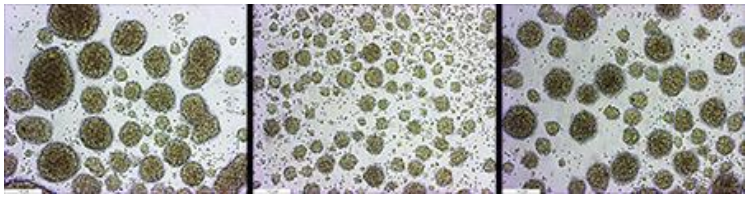
In a pair of papers published January 16, 2020 by *Cell Press*, the researchers also found ways to take advantage of the integrin to both block Zika virus from infecting cells and turn it into something good: a way to shrink brain cancer stem cells.

Integrins are molecules embedded in cell surfaces. They play important roles in cell adherence and communication, and are known to be involved in cancer progression and metastasis. Several other integrins are known entry points for other viruses, including adenovirus, foot-and-mouth disease virus and rotavirus, but αvβ5 was not previously known for its role in viral infections.

Finding the key

One team, led by Tariq Rana, PhD, professor and chief of the Division of Genetics in the Department of Pediatrics at UC San Diego School of Medicine and Moores Cancer Center, used CRISPR gene editing to systematically delete every gene in a 3D culture of human glioblastoma (brain cancer) stem cells growing in a laboratory dish. Then they exposed each variation to Zika virus to determine which genes, and the proteins they encode, are required for the virus to enter the cells. The virus was -- for the first time -- labeled with green fluorescent protein (GFP) to allow the researchers to visualize viral entry into the cells.

Their study, published in *Cell Reports*, uncovered 92 specific human brain cancer stem cell genes that Zika virus requires to infect and replicate in the cells. But one gene stood out, the one that encodes αvβ5 integrin.



3D human brain organoids. Left: normal, uninfected. Center: infected with Zika virus. Right: infected with Zika virus and treated with cilengitide, which protects the cells from destruction by the virus. **UC San Diego Health Sciences**

"Integrins are well known as molecules that many different viruses use as doorknobs to gain entry into human cells," Rana said. "I was expecting to find Zika using multiple integrins, or other cell surface molecules also used by other viruses. But instead we found Zika uses αvβ5, which is unique. When we further examined αvβ5 expression in brain, it made perfect sense because αvβ5 is the only integrin member enriched in neural stem cells, which Zika preferentially infects. Therefore, we believe that αvβ5 is the key contributor to Zika's ability to infect brain cells."

Blocking Zika virus infection

The second study, published in *Cell Stem Cell*, was led by Jeremy Rich, MD, professor in the Department of Medicine at UC San Diego School of Medicine and director of neuro-oncology and of the Brain Tumor Institute at UC San Diego Health. Knowing that many viruses use integrins for entry into human cells, Rich's team inhibited each integrin with a different antibody to see which would have the greatest effect.

"When we blocked other integrins, there was no difference. You might as well be putting water on a cell," said Rich, who is also a faculty member in the Sanford Consortium for Regenerative Medicine and Sanford Stem Cell Clinical Center at UC San Diego Health. "But with αvβ5, blocking it with an antibody almost completely blocked the ability of the virus to infect brain cancer stem cells and normal brain stem cells."

Rich's team followed up by inhibiting αvβ5 in a glioblastoma mouse model with either an antibody or by deactivating the gene that encodes it. Both approaches blocked Zika virus infection and allowed the treated mice to live longer than untreated mice. They also found that blocking the αvβ5 integrin in glioblastoma tumor samples removed from patients during surgery blocked Zika virus infection.

Rana's team also blocked αvβ5 in mice, treating them daily with cilengitide or SB273005, two experimental cancer drugs that target the integrin. Six days after Zika virus infection, the brains of their drug-treated mice contained half as much virus as mock-treated mice.

"The neat thing is that these findings not only help advance the Zika virus research field, but also opens the possibility that we could similarly block the entry of multiple viruses that use other integrins with antibodies or small molecule inhibitors," Rana said.

Rana and team are now engineering a mouse model that lacks αvβ5 integrin in the brain -- a tool that would allow them to definitively prove the molecule is necessary for Zika viral entry and replication.

Leveraging Zika to treat brain cancer

Rich is a neuro-oncologist who specializes in diagnosing and treating patients with glioblastoma, a particularly aggressive and deadly type of brain tumor. When he first saw how the Zika virus shrinks brain tissue, it reminded him of what he hopes to achieve when he's treating a patient with glioblastoma. In 2017, he and collaborators published a study in which they determined that Zika virus selectively targets and kills glioblastoma stem cells, which tend to be resistant to standard treatments and are a big reason why glioblastomas recur after surgery and result in shorter patient survival rates.

Rich's latest study helps account for the virus' preference for glioblastoma stem cells over healthy brain cells. The αvβ5 integrin is made up of two separate subunits -- αv and β5. The team found that glioblastoma stem cells produce a lot of both the αv subunit (associated with stem cells) and β5 subunit (associated with cancer cells). Together, these units form the αvβ5 integrin, which, the team discovered, plays an important role in glioblastoma stem cell survival. Those high levels of αvβ5 integrin also help explain why, in the study, glioblastoma stem cells were killed by Zika virus at much higher rates than normal stem cells or other brain cell types.

"It turns out that the very thing that helps cancer cells become aggressive cancer stem cells is the same thing Zika virus uses to infect our cells," Rich said.

To see how this might play out in a more realistic model of human disease, Rich's team partnered with an expert in human brain disease modeling -- Alysson Muotri, PhD, professor at UC San Diego School of Medicine, director of the UC San Diego Stem Cell Program and a member of the Sanford Consortium for Regenerative Medicine, and team. Pinar Mesci, PhD, a postdoctoral researcher in Muotri's lab, generated a new brain tumor model, where human glioblastoma tumors were transplanted into human brain organoids, laboratory "mini-brains" that can be used for drug discovery. The researchers discovered that Zika virus selectively eliminates glioblastoma stem cells from the brain organoids. Inhibiting αvβ5 integrin reversed that anti-cancer activity, further underscoring the molecule's crucial role in Zika virus' ability to destroy cells.

Now Rich's team is partnering with other research groups to perform targeted drug studies. In addition to searching for drugs to block Zika virus, as Rana's group is doing, Rich is interested in genetic modifications to the virus that could help better target its destruction to brain cancer cells, while leaving healthy cells alone.

"While we would likely need to modify the normal Zika virus to make it safer to treat brain tumors, we may also be able to take advantage of the mechanisms the virus uses to destroy cells to improve the way we treat glioblastoma," Rich said. "We should pay attention to viruses. They have evolved over many years to be very good at targeting and entering specific cells in the body."

Zika virus was perhaps best known in 2015-16, when a large outbreak affected primarily Latin America, but also several other regions of the world. While that particular epidemic has passed, Zika virus has not gone away. Smaller, local outbreaks continue and this past summer, the first few cases of native Zika virus infection were recorded in Europe. Scientists warn Zika could continue to spread as climate change affects the habitat range of the mosquito that carries it. The virus can also be transmitted from pregnant mother to fetus, and via sexual contact. More than half of all people on Earth are at risk for Zika virus infection, and there is no safe and effective treatment or vaccine.

Co-authors of Rana's study, published January 16, 2020 in Cell Reports, *include: Shaobo Wang, Qiong Zhang, Shashi Kant Tiwari, Gianluigi Lichinchi, Edwin H. Yau, Hui Hui, Wanyu Li, UC San Diego; and Frank Furnari, UC San Diego and Ludwig Institute for Cancer Research.*

Co-authors of Rich's study, published January 16, 2020 in Cell Stem Cell, *also include: Zhe Zhu, Jean A. Bernatchez, Xiuxing Wang, Hiromi I. Wettersten, Sungjun Beck, Alex E. Clark, Qiulian Wu, Sara M. Weis, Priscilla D. Negraes, Cleber A. Trujillo, Jair L. Siqueira-Neto, David A. Cheresh, UC San Diego; Ryan C. Gimple, Leo J.Y. Kim, UC San Diego and Case Western Reserve University; Simon T. Schafer, Fred H. Gage, Salk Institute for Biological Studies; Briana C. Prager, UC San Diego, Case Western Reserve University and Cleveland Clinic; Rekha Dhanwani, Sonia Sharma, La Jolla Institute for Allergy and Immunology; Alexandra Garancher, Robert J. Wechsler-Reya, Sanford Burnham Prebys Medical Discovery Institute; Stephen C. Mack, Baylor College of Medicine, Texas Children's Hospital; Luiz O. Penalva, Children's Cancer Research Institute; Jing Feng, Zhou Lan, Rong Zhang, Alex W. Wessel, Michael S. Diamond, Hongzhen Hu, Washington University School of Medicine; Sanjay Dhawan, and Clark C. Chen, University of Minnesota.*

Disclosures: Tariq Rana is a co-founder of, member of the scientific advisory board for, and has equity interest in ViRx Pharmaceuticals. Alysson Muotri is a co-founder and has equity interest in TISMOO, a company dedicated to genetic analysis focusing on therapeutic applications customized for autism spectrum disorder and other neurological disorders. David Cheresh is a co-founder of TargeGen and AlphaBeta Therapeutics, a new but currently unfunded company developing an antibody to integrin αvβ5 involved in cancer treatment. The terms of these arrangements have been reviewed and approved by UC San Diego in accordance with its conflict of interest policies. In addition, Michael Diamond, of Washington University School of Medicine, is a consultant for Inbios and Atreca and serves on the Scientific Advisory Board of Moderna.

http://bit.ly/3ai0Wcm

America's most widely consumed oil causes genetic changes in the brain

Soybean oil linked to metabolic and neurological changes in mice

New UC Riverside research shows soybean oil not only leads to obesity and diabetes, but could also affect neurological conditions like autism, Alzheimer's disease, anxiety, and depression.

Used for fast food frying, added to packaged foods, and fed to livestock, soybean oil is by far the most widely produced and consumed edible oil in the U.S., according to the U.S. Department of Agriculture. In all likelihood, it is not healthy for humans.

It certainly is not good for mice. The new study, published this month in the journal *Endocrinology*, compared mice fed three different diets high in fat: soybean oil, soybean oil modified to be low in linoleic acid, and coconut oil.

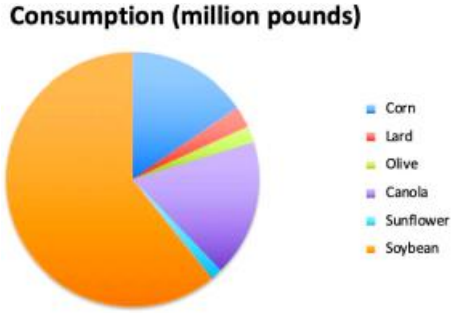
The same UCR research team found in 2015 that soybean oil induces obesity, diabetes, insulin resistance, and fatty liver in mice. Then in a 2017 study, the same group learned that if soybean oil is engineered to be low in linoleic acid, it induces less obesity and insulin resistance.

However, in the study released this month, researchers did not find any difference between the modified and unmodified soybean oil's effects on the brain. Specifically, the scientists found pronounced

effects of the oil on the hypothalamus, where a number of critical processes take place.

"The hypothalamus regulates body weight via your metabolism, maintains body temperature, is critical for reproduction and physical growth as well as your response to stress," said Margarita Curras-Collazo, a UCR associate professor of neuroscience and lead author on the study.

The team determined a number of genes in mice fed soybean oil were not functioning correctly. One such gene produces the "love" hormone, oxytocin. In soybean oil-fed mice, levels of oxytocin in the hypothalamus went down.



Edible fats and oils consumed in the U.S., 2017/18. **USDA**

The research team discovered roughly 100 other genes also affected by the soybean oil diet. They believe this discovery could have ramifications not just for energy metabolism, but also for proper brain function and diseases such as autism or Parkinson's disease. However, it is important to note there is no proof the oil causes these diseases. Additionally, the team notes the findings only apply to soybean oil -- not to other soy products or to other vegetable oils.

"Do not throw out your tofu, soymilk, edamame, or soy sauce," said Frances Sladek, a UCR toxicologist and professor of cell biology. "Many soy products only contain small amounts of the oil, and large amounts of healthful compounds such as essential fatty acids and proteins." A caveat for readers concerned about their most recent meal is that this study was conducted on mice, and mouse studies do not always translate to the same results in humans.

Also, this study utilized male mice. Because oxytocin is so important for maternal health and promotes mother-child bonding, similar studies need to be performed using female mice.

One additional note on this study -- the research team has not yet isolated which chemicals in the oil are responsible for the changes they found in the hypothalamus. But they have ruled out two candidates. It is not linoleic acid, since the modified oil also produced genetic disruptions; nor is it stigmasterol, a cholesterol-like chemical found naturally in soybean oil.

Identifying the compounds responsible for the negative effects is an important area for the team's future research.

"This could help design healthier dietary oils in the future," said Poonamjot Deol, an assistant project scientist in Sladek's laboratory and first author on the study.

"The dogma is that saturated fat is bad and unsaturated fat is good. Soybean oil is a polyunsaturated fat, but the idea that it's good for you is just not proven," Sladek said.

Indeed, coconut oil, which contains saturated fats, produced very few changes in the hypothalamic genes.

"If there's one message I want people to take away, it's this: reduce consumption of soybean oil," Deol said about the most recent study.

http://bit.ly/376GTM0

No shield from x-rays: How science is rethinking lead aprons

Fear of radiation is entrenched in the collective psyche

Mary Chris Jaklevic

CHICAGO — Patients have come to expect a technician to drape their torsos with a heavy lead apron when they get an X-ray, but new thinking among radiologists and medical physicists is upending the decades-old practice of shielding patients from radiation.

Some hospitals are ditching the ritual of covering reproductive organs and fetuses during imaging exams after prominent medical and scientific groups have said it's a feel-good measure that can impair the quality of diagnostic tests and sometimes inadvertently increase a patient's radiation exposure.

The about-face is intended to improve care, but it will require a major effort to reassure regulators, health care workers and the public that it's better not to shield.

Fear of radiation is entrenched in the collective psyche, and many people are surprised to learn that shielding can cause problems. The movement also has yet to gain much traction among dentists, whose offices perform more than half of all X-rays.

"There's this big psychological component, not only with patients but with staff," said Rebecca Marsh, a medical physicist at the University of Colorado Anschutz Medical Campus in Aurora, Colorado, who spoke about shielding at a December forum here at the annual meeting of the Radiological Society of North America. "How do you approach something that is so deeply ingrained in the minds of the health care community and the minds of patients?"

Covering testicles and ovaries during X-rays has been recommended since the 1950s, when studies in fruit flies prompted concern that radiation might damage human DNA and cause birth defects. Only in the past decade did radiology professionals start to reassess the practice, based on changes in imaging technology and a better understanding of radiation's effects.

Lead shields are difficult to position accurately, so they often miss the target area they are supposed to protect. Even when in the right place, they can inadvertently obscure areas of the body a doctor needs to see — the location of a swallowed object, say — resulting in a need to repeat the imaging process, according to the American Association of Physicists in Medicine, which represents physicists who work in hospitals.

Shields can also cause automatic exposure controls on an X-ray machine to increase radiation to all parts of the body being examined in an effort to "see through" the lead.

Moreover, shielding doesn't protect against the greatest radiation effect: "scatter," which occurs when radiation ricochets inside the body, including under the shield, and eventually deposits its energy in tissues.

Still, Dr. Cynthia Rigsby, a radiologist at Chicago's Ann & Robert H. Lurie Children's Hospital, called the move away from shielding a "pretty substantial" change. "I don't think it's going to happen overnight," she added.

Sweeping shift

In April, the physicists' association recommended that shielding of patients be "discontinued as routine practice." Its statement was endorsed by several groups, including the American College of Radiology and the Image Gently Alliance, which promotes safe pediatric imaging.

Around the same time, the Food and Drug Administration proposed removing from the federal code a 1970s recommendation to use shielding. A final rule is expected in September.

In the coming year, the National Council on Radiation Protection and Measurements, which gives guidance to regulatory bodies, is expected to release a statement supporting a halt to patient shielding. However, experts continue to recommend that health care workers in the imaging area protect themselves with leaded barriers as a matter of occupational safety.

Groups in Canada and Australia have endorsed the change, and a movement to abandon lead shields is underway in Great Britain, according to Marsh.

Marsh, who's helping direct the educational effort, said perhaps a dozen U.S. hospitals have changed their official policies, but "most hospitals are starting to have the conversation."

Chicago's Lurie hospital is launching an "Abandon the Shield" campaign to educate staff, patients and caregivers before it stops shielding across the organization this spring, Rigsby said. Shielding is used for most of the 70,000 X-ray procedures performed annually

at Lurie in a variety of settings, from orthopedics to the emergency department.

A few miles away, at the University of Chicago Medicine hospitals, the recommendation to stop shielding "came as kind of a shock," said Dr. Kate Feinstein, chief of pediatric radiology.

Feinstein said it seems contrary to what radiology professionals are taught, and she's uncertain how it applies to her department, which already takes steps to reduce the chance that a shield will interfere with an exam. "We apply our shields correctly, and our technologists are incredibly well trained," she said.

Nevertheless, Feinstein said, her department is weighing a halt to routine shielding.

Some hospitals are concerned about violating state regulations. As of last spring, at least 46 states, including Illinois, required shielding of reproductive organs if they are close to the area being examined, unless shielding would interfere with the diagnostic quality of the exam, according to the medical physicists' association. Some states are revising their regulations. In some cases, hospitals have applied for waivers or sidestepped state rules by taking the stance that a shield has the potential to affect diagnostic quality anytime it is used, Marsh said.

No evidence of benefit

The amount of radiation needed for an X-ray is about one-twentieth of what it was in the 1950s, and scientists have found no measurable harm to ovaries and testicles of patients from radiation exposure that comes from diagnostic imaging after decades of looking at data.

"What we know now is that there is likely no [hereditary] risk at all," said Dr. Donald Frush, a radiologist at Lucile Packard Children's Hospital Stanford in Palo Alto, California, who chairs the Image Gently Alliance.

There's also no evidence that fetuses are harmed by even a relatively high amount of radiation exposure, such as that from a CT scan of the abdomen, Marsh said.

Nevertheless, some patients may insist on shielding. The physicists' group suggested that when hospitals craft their policies they consider that shielding may "calm and comfort."

"I don't think any of us are advocating to never use it," Frush said.

A need for outreach

Public confusion might develop if dentists continue to shield while hospitals don't. An estimated 275 million medical X-ray exams were performed in the U.S. in 2016, but 320 million dental X-rays were done.

Mahadevappa Mahesh, the chief physicist at Johns Hopkins Hospital, said there's been less outreach to dentists on the topic. "It's high time we bring them into the discussion," he said.

The American Dental Association states abdominal shielding "may not be necessary" but has continued to recommend using lead collars to shield the thyroid "whenever possible."

But Mahesh, who's on the board of the physicists' association, cautioned that lead collars to protect the thyroid may not be helpful and could obscure images taken by newer 3D dental imaging machines.

Contacted for a response, the dental association said its guidance on shielding is under review.

Technologists especially will need support in educating patients and families "so they are not feeling like they are walking into a disastrous conversation," said Marsh, the medical physicist.

She is doing her part. At the radiology conference, Marsh strummed a banjo and sang her version of the Woody Guthrie ballad "So Long, It's Been Good to Know Yuh," with lyrics like: "To get rid of shielding at first may seem strange, but the time is upon us to embrace this change."

http://bit.ly/2R7qhF1

Human-caused biodiversity decline started millions of years ago

The human-caused biodiversity decline started much earlier than researchers used to believe.

According to a new study published in the scientific journal *Ecology Letters* the process was not started by our own species but by some of our ancestors.

The work was done by an international team of scientists from Sweden, Switzerland and the United Kingdom. The researchers point out in the study that the ongoing biological diversity crisis is not a new phenomenon, but represents an acceleration of a process that human ancestors began millions of years ago.

"The extinctions that we see in the fossils are often explained as the results of climatic changes but the changes in Africa within the last few million years were relative minor and our analyses show that climatic changes were not the main cause of the observed extinctions," explains Søren Faurby, researcher at Gothenburg University and the main author of the study.

"Our analyzes show that the best explanation for the extinction of carnivores in East Africa is instead that they are caused by direct competition for food with our extinct ancestors," adds Daniele Silvestro, computational biologist and co-author of the study.

Carnivores disappeared

Our ancestors have been common throughout eastern Africa for several million years and during this time there were multiple extinctions according to Lars Werdelin, co-author and expert on African fossils.

"By investigating the African fossils, we can see a drastic reduction in the number of large carnivores, a decrease that started about 4 million years ago. About the same time, our ancestors may have started using a new technology to get food called kleptoparasitism," he explains. Kleptoparasitism means stealing recently killed animals from other predators. For example, when a lion steals a dead antelope from a cheetah.

The researchers are now proposing, based on fossil evidence, that human ancestors stole recently killed animals from other predators. This would lead to starvation of the individual animals and over time to extinction of their entire species.

"This may be the reason why most large carnivores in Africa have developed strategies to defend their prey. For example, by picking up the prey in a tree that we see leopards doing. Other carnivores have instead evolved social behavior as we see in lions, who among other things work together to defend their prey," explains Søren Faurby

Humans today affect the world and the species that live in it more than ever before. "But this does not mean that we previously lived in harmony with nature. Monopolization of resources is a skill we and our ancestors have had for millions of years, but only now are we able to understand and change our behavior and strive for a sustainable future. 'If you are very strong, you must also be very kind'," concludes Søren Faurby and quotes Astrid Lindgrens book about Pippi Longstocking.

Title: Brain expansion in early hominins predicts carnivore extinctions in East Africa
Digital publication: https://onlinelibrary.wiley.com/doi/10.1111/ele.13451

http://bit.ly/3790mvx

The Lancet: Fewer than half of US clinical trials have complied with the law on reporting results, despite new regulations

Compliance remains poor, and is not improving, with US Government sponsored trials most likely to breach

January 2020 is the third anniversary of the implementation of the new US regulations that require clinical trials to report results within one year of completion (Final Rule of the FDA Amendments

Act)--but compliance remains poor, and is not improving, with US Government sponsored trials most likely to breach.

Less than half (41%) of clinical trial results are reported promptly onto the US trial registry, and 1 in 3 trials remain unreported, according to the first comprehensive study of compliance since new US regulations came into effect in January 2017.

The findings, published in *The Lancet*, indicate that trials with non-industry sponsors (such as universities, hospitals, and governments) are far more likely to breach the rules than trials sponsored by industry [1]--with US Government sponsored trials least likely to post results on time at the world's largest clinical trial registry, ClinicalTrials.gov.

It has been known for several decades that the results of clinical trials are often not fully reported. To improve public disclosure, and limit selective publishing of results, the US Food and Drug Administration Amendment Act (FDAAA) of 2007 requires sponsors of most US-regulated clinical trials to register and report results on ClinicalTrials.gov within 12 months of primary completion, irrespective of whether the results are positive or negative.

A subsequent 'Final Rule' to the Act took effect in January, 2017. This introduced clearer reporting requirements including fines of up to US$10,000 a day for non-compliance (now US$ 12,103 inflation adjusted). National Institute of Health (NIH) leaders said that the Final Rule would result in "rapid increases" in the percentage of trials registered and shared on the US registry [2].

The authors say that the high rates of non-compliance found in the new study likely reflect the lack of enforcement by regulators, and they call for trial sponsors to be held to account by the FDA.

"Patients and clinicians cannot make informed choices about which treatments work best when trial results are routinely withheld. Clinical trials are not abstract research projects: they are large, expensive, practical evaluations that directly impact on patient care by informing treatment guidelines and evidence reviews." says Dr Ben Goldacre from Oxford University, UK, who led the research. [3]

He continues: "Sponsors are breaching their legal obligations, but also their ethical obligations to the patients who generously participate in clinical trials. Our study has identified over 2,400 trials breaching the rules, but to our knowledge the FDA has never levied a single fine or other enforcement action, despite all the levers available to them. Compliance will only improve when action is taken." [3]

Non-reporting of clinical trial results has been well documented since the 1980s, especially those trials finding no evidence of effectiveness for the treatment being tested [4]. However, failing to disclose trial results threatens the integrity of the evidence base of all clinical medicine, breaches participants' trust, and wastes valuable research resources.

The first trials covered by the Final Rule were due to report in January 2018. To investigate the extent of compliance with these new reporting requirements, the researchers examined all 4,209 trials registered on ClinicalTrials.gov that were legally required to report results between March 2018 and September 2019. They also assessed trends in compliance, factors associated with compliance, and ranked individual sponsors according to their level of compliance.

Of the completed trials included in the study, around half (52%; 2,178) had non-industry sponsors, most involved a drug intervention (71%; 2,968), and most were solely conducted in the USA (71%; 3,000).

Analyses found that only 41% (1,722/4,209) of completed clinical trials reported results within the one year legal deadline, whilst 36% (1,523/4,209) still had not been reported by September 16, 2019. Moreover, progress has stalled--the proportion of compliant trials

has remained stable since July 2018. The median delay from completion to submitting results was 424 days--59 days higher than the legal reporting requirement of one year (figure 1).

Trials with an industry sponsor were much more likely to comply with the law than those with a non-industry or US Government sponsor (50% vs 34% vs 31% trials submitted in time).Better performance was also seen among sponsors with more experience of running large numbers of trials, when compared with those who have only ever run a very small number of projects (66% vs 21% trials submitted in time; table 3). Encouragingly, the authors say, this suggests that "research experience and robust internal governance processes can contribute to improved performance."

Further analyses estimate that had the law been strictly enforced, over US$4 billion in fines could have been collected up to the end of September 2019.

"Over four decades since non-reporting of clinical trials was first reported, it is disappointing to see that we have only progressed to legislation being passed, and then largely ignored," says co-author Nicholas DeVito from the University of Oxford, UK. "The fact that the US Government cannot comply with its own laws is particularly concerning." [3]

He continues: "Until effective enforcement action is taken, public audit may help. We have established an openly accessible public website at fdaaa.trialstracker.net where fresh data on compliance with FDAAA will be posted every day, identifying each individual overdue trial, and compliance statistics for each individual sponsor. We hope this will help to incentivise sponsors, and provide useful targeted information for all those who aim to comply with the law." [3]

The authors note that they only examine the availability of results on ClinicalTrials.gov as required by the law, and not the quality of the results or their availability elsewhere.

Writing in a linked Comment, lead author Dr Erik von Elm (who was not involved in the study) from the University of Lausanne in Switzerland points out that, "any law is only as good as its enforcement", adding that, "if this rule were to be enforced, academic sponsors would probably make substantial efforts to reduce the number of non- or late-reported trials and to improve data quality. Training, auditing and incentive mechanisms could be overseen by dedicated staff. A senior "transparency officer" versed in trial conduct and reporting could take a proactive mentoring role and help investigators overcome barriers that currently prevent them from timely reporting of trial results in registries. If completeness of reporting was a criterion in individual academic evaluations, this could have a considerable "signalling effect" within the local research community."

This study was funded by the Laura and John Arnold Foundation. It was conducted by researchers from Oxford University, UK.

The labels have been added to this press release as part of a project run by the Academy of Medical Sciences seeking to improve the communication of evidence. For more information, please see: http://www.sciencemediacentre.org/wp-content/uploads/2018/01/AMS-press-release-labelling-system-GUIDANCE.pdf if you have any questions or feedback, please contact The Lancet *press office pressoffice@lancet.com*

[1] A sponsor refers to the organisation or person who initiates the study and who has authority and control over the study. They may or may not also be the funder.

[2] https://jamanetwork.com/journals/jama/article-abstract/2553888

[3] Quotes direct from authors and cannot be found in text of Article.

[4] https://www.nejm.org/doi/pdf/10.1056/NEJMsa065779

http://bit.ly/30KAHHr

Can You 'Catch' Cancer or Obesity from Other People?

Noncommunicable diseases cannot pass between people — or can they?

By Nicoletta Lanese - Staff Writer

Our ancestors of yore were plagued by recurrent bouts of malaria, deadly tuberculosis infections, constant syphilis outbreaks and bacteria-laced wounds that never healed. But armed with vaccines and antibiotics, modern-day humans can now avoid or be treated

for these and many other communicable diseases — illnesses caused by infectious agents that can be transmitted between people or from animals to people.

Nowadays, most people don't die from communicable diseases but rather those that cannot be passed on to other people. About 41 million people worldwide die each year from cardiovascular disease, cancer, respiratory disease, diabetes or another chronic illness; noncommunicable diseases account for more than 70% of all deaths globally, according to the World Health Organization.

By definition, noncommunicable diseases are thought to arise from a combination of genetic, environmental and lifestyle factors rather than being transmitted by bacteria, fungi or viruses. In recent years, however, scientists have realized that the collection of microbes crawling in and on the human body — known as the microbiome — has a large influence on our health. Could it be that noncommunicable diseases can actually pass between people via the mighty microbiome?

Some scientists think the answer is yes.

Communities of microbes make their abode in the human body, and research suggests that these bugs help direct the function of various physiological systems, including metabolism, digestion and immune defense. Scientists don't yet fully understand what distinguishes a healthy microbiome from an unhealthy one, but certain diseases do seem to be linked to a bacterial imbalance in the body.

For instance, people with diabetes, inflammatory bowel disease and cardiovascular disease tend to host a different collection of bacteria in their guts than those without the diseases, according to a report published Jan. 16 in the journal Science. The paper suggests that healthy people could potentially "catch" aspects of these ailments through exposure to these mixed-up microbes.

"It is a radical thought to think that [noncommunicable diseases] might actually be communicable, and [this hypothesis] gives us a whole new way of thinking about these diseases," author B. Brett Finlay, a microbiologist at The University of British Columbia in Vancouver, told Live Science in an email. Several recent studies led Finlay and his colleagues to formulate this hypothesis, but a 2019 study conducted in Fiji really "tipped the scales," he said.

In that study, researchers collected saliva and stool samples from about 290 people living in close proximity to determine the types of bacteria that appeared in their mouths and guts. The results, published in March 2019 in the journal Nature Microbiology, revealed distinct patterns of bacterial transmission within each community, particularly among people living in the same household. While mothers and their children shared many microbes, the microbiomes of spouses seemed to share the most similarities. The team could even predict which study participants were paired up as a couple based on their microbiomes alone.

The Fiji study suggests that at least some elements of the microbiome can be passed between people. But could the transmitted bugs actually drive disease? Quite possibly.

Spouses of people with type 2 diabetes, for example, stand a higher chance of developing the disease themselves within a year of their partner's diagnosis, Finlay noted. In an animal model of the disease, germ-free mice developed diabetic symptoms after receiving a bacteria-laden fecal transplant from a diseased mouse. Similar trends have been uncovered in inflammatory bowel disease, both in human spouses and animal models.

Even cardiovascular disease may be linked to the presence of particular bacteria in the gut, Finlay noted. Certain microbes produce an enzyme that breaks red meat down into a compound called trimethylamine N-oxide (TMAO). People with high concentrations of TMAO in their blood have a high chance of

developing cardiovascular disease, and their risk rises if these enzyme-producing bacteria appear in their gut.

Studies show that the bacteria can induce cardiovascular disease if transferred from a human into a mouse, but it's unknown whether the same might occur between people.

Testing the idea

Additional studies hint that more noncommunicable diseases may be influenced by bacteria and that those bacteria may travel between people. "Our lab has shown that early-life microbes impact hugely on asthma ... and we have some very exciting preliminary data with Parkinson's," Finlay said. Microbes also alter immune function, which may prove relevant to cancer patients whose immune systems fail to recognize and attack tumors in the body, he added.

Obesity, a major risk factor for noncommunicable diseases, also involves potentially transmittable microbes. Lean mice become obese when they receive a fecal transplant from already-obese mice, while humans with obese friends or siblings stand a higher chance of being obese than those who don't have obese friends or siblings. Living in a country with a high obesity rate also raises a person's risk of being obese.

But all of these studies raise a similar question:How can scientists tell which aspects of a disease might be linked to troublesome microbes, as opposed to diet, exercise, genes or environmental factors?

This is a hard question to answer, Finlay said. "Ideally, one does a fecal transfer from a diseased person into a healthy one and causes disease, but of course this can't be done [for ethical reasons]," he said. To test his hypothesis, Finlay and his colleagues will have to rely on animal models and population studies akin to the one conducted in Fiji. If any noncommunicable diseases can be transmitted through microbes, the bugs will meet three criteria: They will appear distinct in diseased people versus healthy people; they will be able to be isolated from a disease host; and they will induce disease when transferred into healthy animals.

"As we identify mechanisms further, we can actually test these mechanisms, inhibit them ... and really show microbes are involved," Finlay said.

Once scientists clarify how and whether noncommunicable diseases hop between people, they can develop treatments to "correct" diseased microbiomes. Some companies have already begun developing so-called second generation probiotics for inflammatory bowel disease, concocted from a mixture of microbes designed to rebalance the gut microbiome, Finlay said. Dietary changes, pharmaceuticals and, in extreme cases, fecal transplants could also serve as potential treatment options. Fecal transplants involve placing poop from a healthy donor into the colon of another person in order to revitalize their collection of gut bacteria.

"'Repopulating' people with lab-grown mixtures of microbes is probably better [than using fecal transplants], as we know exactly what is going in and don't have to worry about some virus that we haven't discovered yet being transplanted," Finlay said. Fecal transfers will be licensed only for fixing "serious diseases," as the procedure would have to be repeated numerous times, he added.

Scientists still have a lot to learn about how our in-house bacteria shape our health. A slew of fungi and viruses also live in the human body and may offer an additional route for "noncommunicable" diseases to pass from person to person. If Finlay's hypothesis garners support over time, it could lead to an entirely new understanding of noncommunicable disease.

"It has significant public health policy implications," Finlay said, "and further suggests that looking after your own microbes will not only benefit you but also people close to you."